



Regulatory Affairs Department Australia/New Zealand
Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Australia

6 February 2024

Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
Woden, ACT 2606

Dear Sir/Madam,

Re: Safety-Related Request (SRR) under s.9D(2) and Minor Editorial Changes to the product information under s. 9D(3) of the Therapeutic Goods Act 1989

PION: PI – make safety related changes no data

PIME: PI – make minor editorial changes

Submission Identifier: PM-5
eSubmission Identifier: e001209
Sequence Number: 0041
Related Sequence Number: 0041

AUST R	Product Name (s)
12300 & 401610	DEPO-PROVERA medroxyprogesterone acetate 150 mg/ mL injection vial & pre-filled syringe
44464	DEPO-RALOVERA medroxyprogesterone acetate 150 mg/1 mL injection vial
42932, 42933, 42934, 42935, 12331, 12333, 12334 & 12336	PROVERA medroxyprogesterone acetate 2.5 mg, 5 mg, 10 mg (blister), 10 mg (bottle), 100 mg, 200 mg, 250 mg & 500 mg tablets
46527, 46531, 46532 & 46534	RALOVERA medroxyprogesterone acetate 2.5 mg, 5 mg, 10 mg (blister), 10 mg (bottle) tablets
167889	SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe
401897	SAYANA PRESS medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection ampoule with attached needle

Pfizer Australia Pty Ltd (Client ID: 405) is submitting this application to update the Product Information (PI) for the above products.

Proposed changes

- Addition of a warning regarding meningioma to Section 4.4 Special warnings and precautions for use to all product PIs:

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

- Minor editorial changes including correction to spelling and update in the Sponsor website address which are specific to each product PI.

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Supporting documents

Clean and tracked copies of the proposed PIs are provided in Module 1.3.1.1 and 1.3.1.2.

Copies of the approved Depo-Provera PI (dated 3 May 2023, approved in submission PM-2022-05666-1-5), Depo-Ralovera PI (dated 27 April 2023, approved in submission PM-2023-01608-1-5) and Sayana Press PI (dated 9 August 2023, approved in submission PM-2022-02475-1-5) is provided in this sequence.

Assurances

Pfizer provides assurance that no other changes have been made to the product information other than those detailed above.

CTD Dossier and Content

Electronic media type	Zip file attached to PMMV file.
Virus free statement	The electronic dossier is virus free.
Virus checker	Crowdstrike 6.26.14003.0C
Validation	LORENZ eValidator Version 23.1
Issues in validation report	Pfizer acknowledges the warning message for using the operation 'new' for Module 1.3.1.3. The use of 'new' operation is justified as we are providing the approved Sayana Press PI dated 9 August 2023 as a new leaf.

An electronic funds transfer of the relevant fee will be made upon receipt of an invoice for this application. If you have any further queries relating to this application, please do not hesitate to contact me.

Yours faithfully,

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Pfizer Australia Pty Ltd

Tel: s22

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Australian Government

Department of Health and Aged Care
Therapeutic Goods Administration

Application ID: PM-2024-MV-00766-1
Date: 01-Feb-2024
Status: Passed validation
Applicant Reference:
2402_SRR_MEC_medroxyprogsterones
eSubmission Id: e001209

Applicant Information

Applicant: Pfizer Australia Pty Ltd

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Phone number: §22

Email: §22@pfizer.com

Billing address (Sponsor): Level 17 151 Clarence Street NSW AU

Regulatory correspondence address: Level 17 151 Clarence Street NSW AU

Fee Item: 2A(a), Legislative Basis: 9D(3)

Group: Product Information (PI)
Category: Minor Editorial Changes
Type: PIME: PI - Make minor editorial changes
Assurances: A clean and marked-up copy of the draft revised PI is provided.
Assurance is given that the only changes being requested are those identified in this request.
Details of the changes are provided and they meet the definition of minor editorial changes.
Relevant justification and evidence is provided.
Legislative Basis: 9D(3)
Comment:
Selected ARTG IDs: 12300, 12331, 12333, 12334, 12336, 42932, 42933, 42934, 42935, 44464, 46527, 46531, 46532, 46534, 167889, 401610, 401897

Fee Item: 2A(a), Legislative Basis: 9D(2)

Group: Product Information (PI)
Category: Safety Related Request not requiring the submission of data for evaluation
Type: PION: PI - Make safety related changes no data
Assurances: A clean and marked-up copy of the draft revised PI is provided.
A justification for the proposed variation is provided.
Assurance is given that the only changes being requested are those identified in this request.
Details of the safety-related request are provided.
No evaluation of data is required for this request.
Legislative Basis: 9D(2)
Comment:
Selected ARTG IDs: 12300, 12331, 12333, 12334, 12336, 42932, 42933, 42934, 42935, 44464, 46527, 46531, 46532, 46534, 167889, 401610, 401897

Supporting Information

Fee(s)

Variation group	Legislative basis	Fee Item	Fee \$	Will a new ARTG Id be generated as a result of this submission?
Product Information (PI)	9D(2),9D(3)	2A(a)	\$1900	No

Warning Message(s)

s22

Document generated 1/02/2024 22:53 PM

Lifecycle Management Tracking Table

DEPO-PROVERA® (medroxyprogesterone acetate) 150 mg/mL injection, vial, AUST R 12300.

DEPO-PROVERA® (medroxyprogesterone acetate) 150 mg/mL injection, pre-filled syringe, AUST R 401610

DEPO-RALOVERA® (medroxyprogesterone acetate) 150 mg/mL injection, vial, AUST R 44464.

SAYANA® (medroxyprogesterone acetate) 104 mg/ 0.65mL injection, vial, AUST R 167889

SAYANA PRESS medroxyprogesterone acetate 104 mg/0.65 injection, ampoule with attached needle, AUST R 401897

PROVERA® (medroxyprogesterone acetate) 10 mg (bottle and blister), 5mg, 2.5 mg, 500 mg, 250 mg, 200 mg, 100 mg tablets,

AUST R 42935, 42934, 42933, 42932, 12336, 12334, 12333, 12331

RALOVERA® (medroxyprogesterone acetate) 10 mg (bottle and blister), 5 mg, 2.5 mg tablets, AUST R 46534, 46532, 46531, 46527

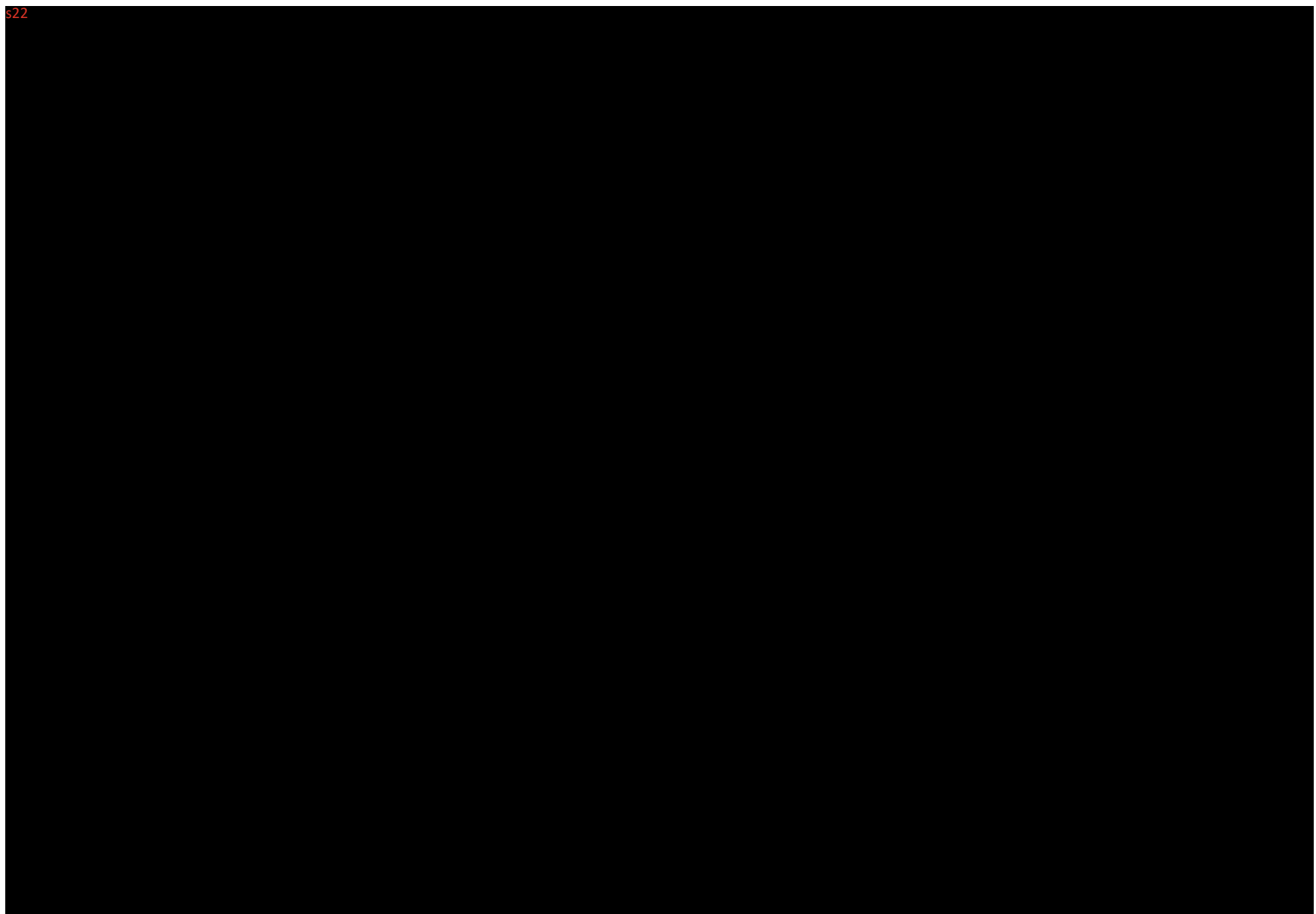
E-submission identifier: e001209

Sequence	Sequence Type	Sequence Description	Related Sequence
0041	seq-type-54 9D(2) - Safety Related Request	seq-desc-2 Initial Addition of warning regarding meningioma	N/a

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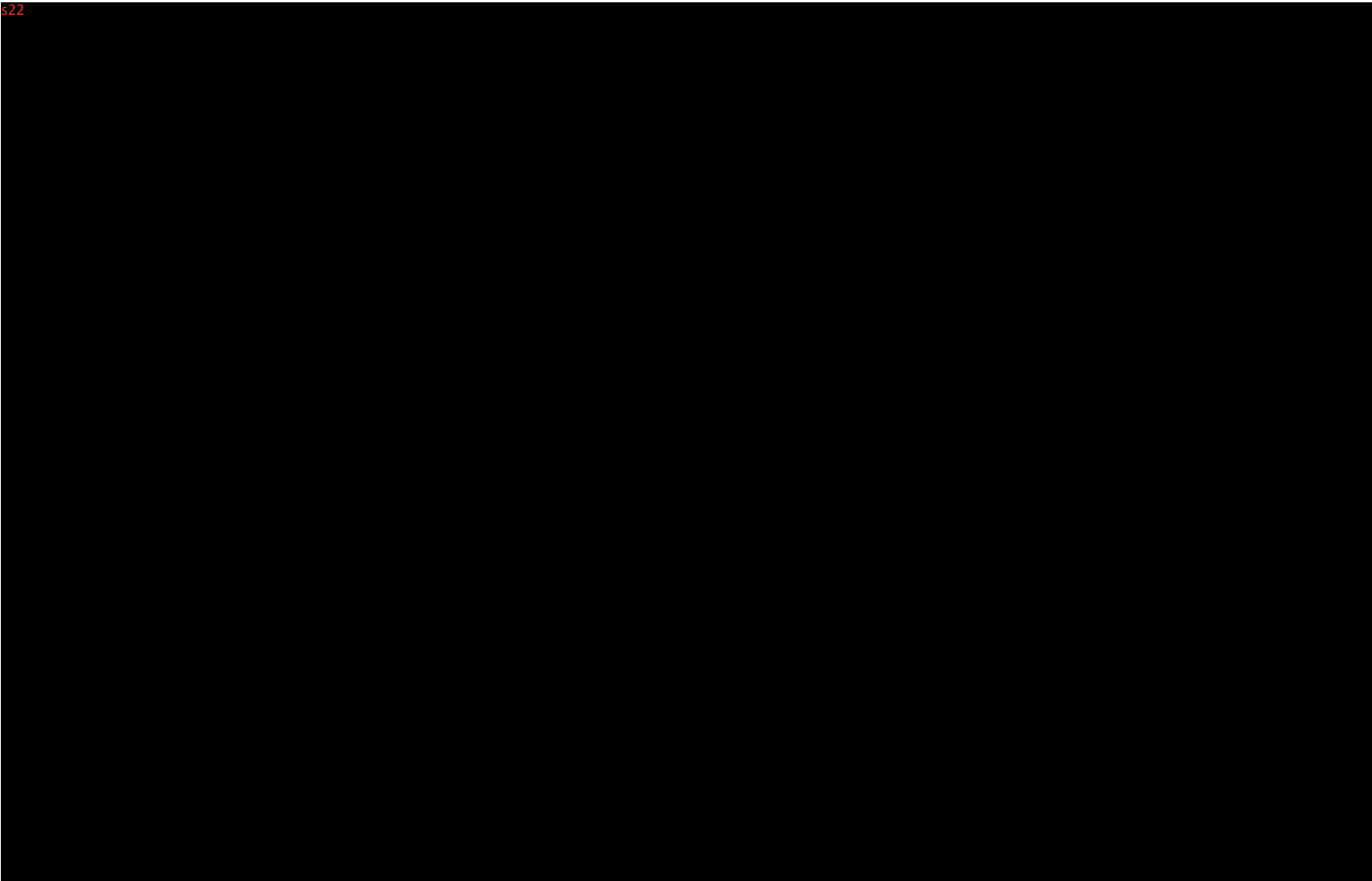
Depo-Provera, Depo-Ralovera, Provera, Ralovera, Sayana
Module 1.0.2 tracking

s22



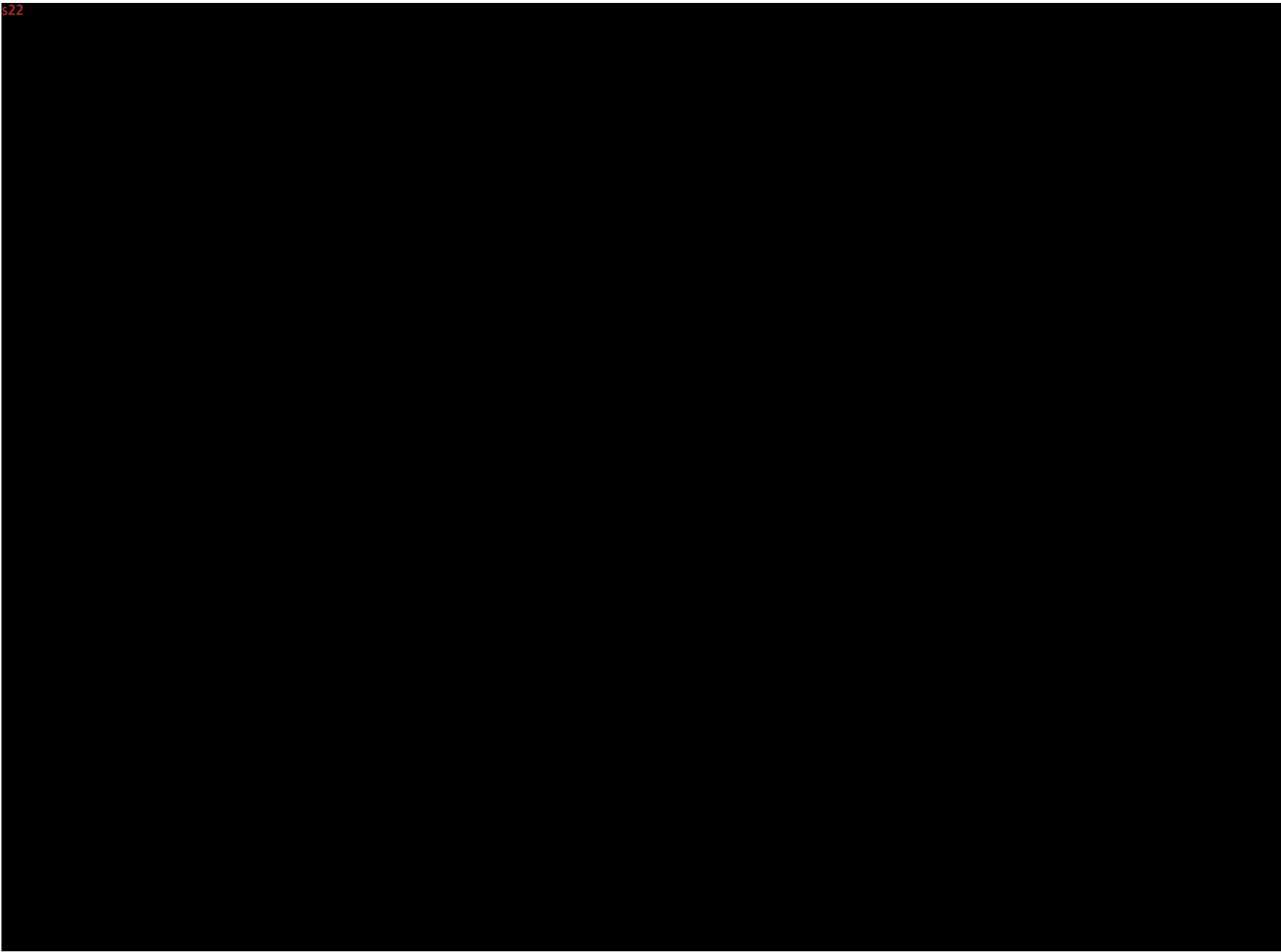
Depo-Provera, Depo-Ralovera, Provera, Ralovera, Sayana
Module 1.0.2 tracking

s22



Depo-Provera, Depo-Ralovera, Provera, Ralovera, Sayana
Module 1.0.2 tracking

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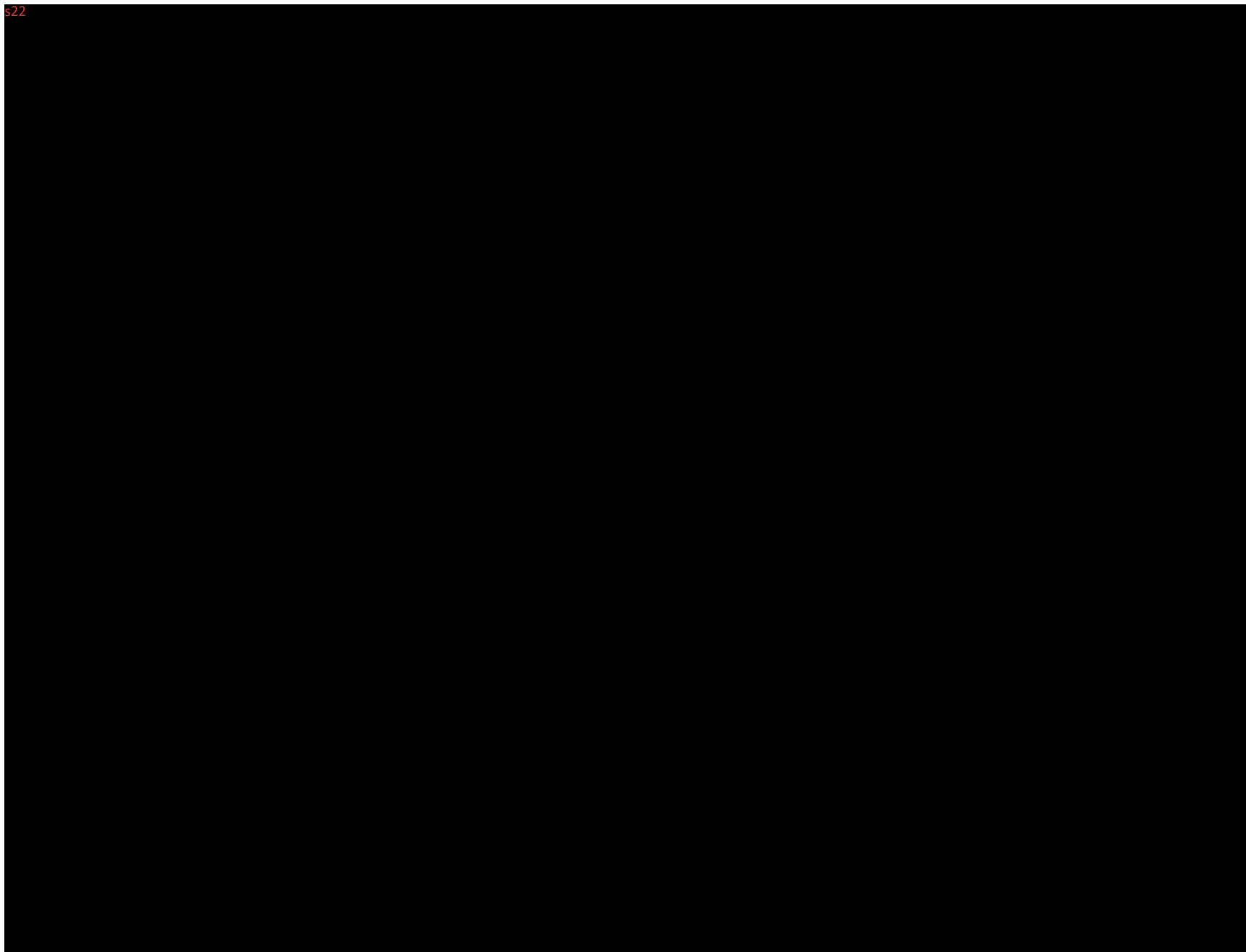


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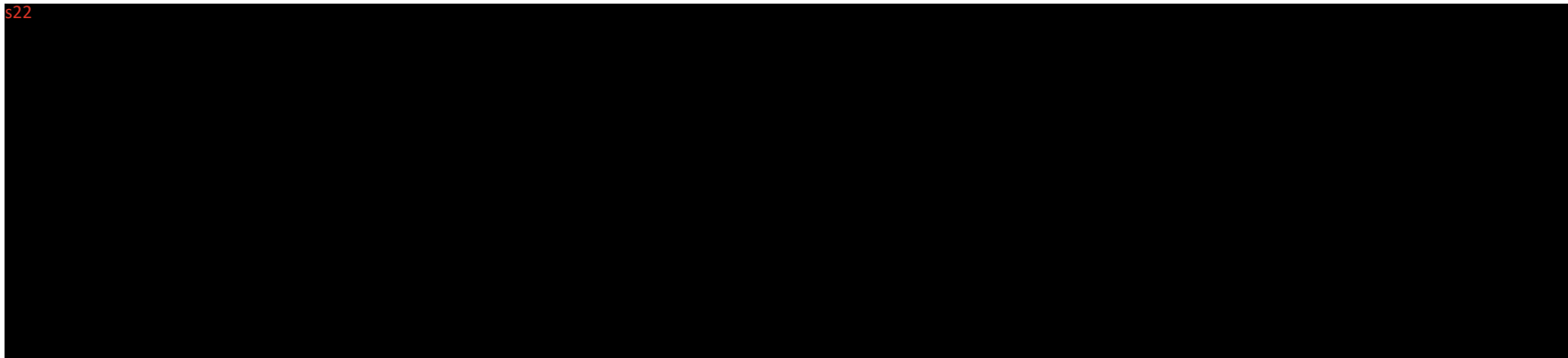
Depo-Provera, Depo-Ralovera, Provera, Ralovera, Sayana
Module 1.0.2 tracking

s22



Depo-Provera, Depo-Ralovera, Provera, Ralovera, Sayana
Module 1.0.2 tracking

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AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-PROVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use MPA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented **S22**: SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or

is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-PROVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By ~~at~~Month 12, amenorrhoea was reported by 57% of women, and by ~~at~~Month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).

DEPO-PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or -corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease

- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-PROVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO PROVERA may significantly decrease the serum concentration of MPA. -DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use – Return of fertility.

Use in pregnancy – Pregnancy Category D

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. In mothers who are breastfeeding and who are treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

- *Cardiac disorders:* Palpitations, myocardial infarction, congestive heart failure.
- *Endocrine disorders:* Prolonged anovulation, Cushingoid syndrome.
- *Eye disorders:* Retinal embolism and thrombosis, diabetic cataract, visual impairment.
- *Gastrointestinal:* Abdominal distension, nausea, constipation, diarrhoea, dry mouth.
- *General disorders and administrative site conditions:* Fatigue, injection site reactions, malaise, hyperpyrexia.
- *Hepatobiliary disorders:* Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
- *Immune system disorders:* Anaphylactic reactions, anaphylactoid reactions, angioedema.
- *Investigations:* Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.
- *Metabolic and nutritional disorders:* Exacerbation of diabetes mellitus, hypercalcaemia.
- *Musculoskeletal and connective tissue disorders:* Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

- *Nervous System disorders:* Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.
- *Psychiatric disorders:* Depression, insomnia, nervousness.
- *Renal and urinary system disorders:* Glycosuria.
- *Reproductive and breast disorders:* Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary embolism.
- *Skin and subcutaneous tissue disorders:* Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.
- *Vascular disorders:* Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash

- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

- Blood and lymphatic system disorders: Blood dyscrasia, anaemia.
- Cardiac disorders: Tachycardia, chest pain.
- Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.
- General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.
- Hepatobiliary disorders: Jaundice, jaundice cholestatic.
- Immune systems disorders: Drug hypersensitivity reactions.
- Metabolism and nutrition disorders: Changes in appetite.
- Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.
- Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.
- Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.
- Renal and urinary disorders: Genitourinary infections.
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.
- Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.
- Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.
- Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial.
- 1 x 1 mL pre-filled syringe.

Not all presentations may be marketed.

6.6 Special precautions for disposal

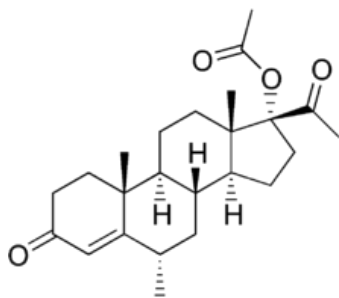
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

Commented **S22** : Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CMI.

10. DATE OF REVISION

03 May 2023DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
~~6.4~~	~~Updated special precautions for storage, ‘Do not refrigerate or freeze’.~~
~~6.5~~	~~Updated description for the pre-filled syringe presentation and information on marketed presentations.~~
<u>4.4</u>	<u>Addition of information regarding meningioma</u> <u>Minor editorial changes</u>
<u>8</u>	<u>Update to sponsor website address</u>

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AUSTRALIAN PRODUCT INFORMATION – DEPO-RALOVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented **S22**: SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or

is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By ~~at~~Month 12, amenorrhoea was reported by 57% of women, and by ~~at~~Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-RALOVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-RALOVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated ~~when~~ DEPO-RALOVERA is used long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-RALOVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or -corticosteroids

Commented ~~S22~~ : Minor editorial change

- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-RALOVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-RALOVERA in women who were first exposed before the

age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-RALOVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes

should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-RALOVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-RALOVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-RALOVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-RALOVERA. Therefore, if such tests are abnormal in a patient taking DEPO-RALOVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-RALOVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased

- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA. -DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use - Return of fertility

Use in pregnancy – Pregnancy Category D

DEPO-RALOVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-RALOVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-RALOVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period

- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-RALOVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression

- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events reported by fewer than 1% of subjects:

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobiliary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

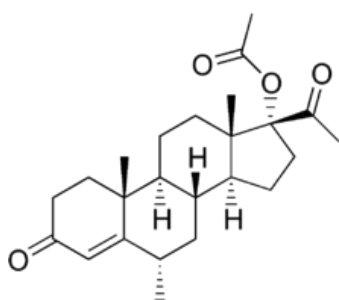
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

Commented s22 : Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CML.

9. DATE OF FIRST APPROVAL

31 May 1993-

10. DATE OF REVISION

~~27 April 2023~~[DD Month YYYY](#)

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
~~Throughout~~	~~Minor editorial changes~~
~~6.4~~	~~Updated special precautions for storage, ‘Do not refrigerate or freeze’.~~
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – SAYANA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA 104 mg/0.65 mL suspension for injection syringe contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

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Excipient(s) with known effect

SAYANA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg MPA in 0.65 mL suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra indicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA must be given by subcutaneous injection (SC MPA) into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). SAYANA is not formulated for intramuscular (IM) injection.

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It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: pre-filled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from ~~intramuscular (IM)~~ MPA (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for IM MPA (150 mg).

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BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties – Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment

Renal impairment

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use

Route of administration

SAYANA is not formulated for IM injection. SAYANA must be given by SC injection.

Physical examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical Trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control

group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86% , -4.11% , -4.89% , -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1: Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with MPA 150 mg IM and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received MPA injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received MPA Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during ~~the~~Month 6 and 56.5% experienced amenorrhoea during ~~the~~Month twelve.

-

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

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Figure 1: Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies.

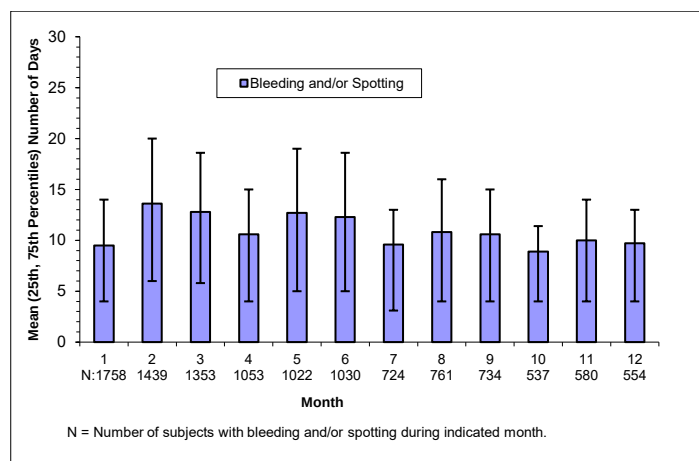
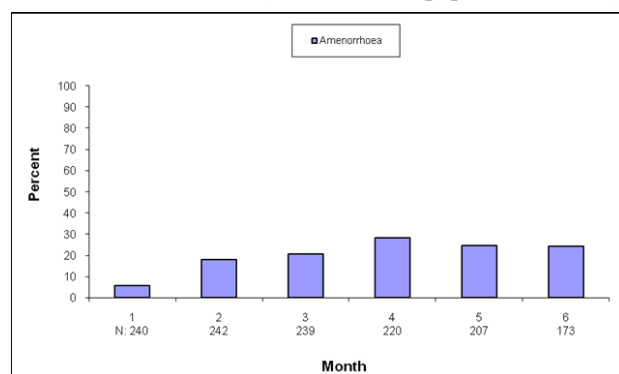


Figure 2: Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289).



Cancer risks

Long-term case-controlled surveillance of depot MPA IM 150 mg use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the

previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A ~~R~~relative ~~R~~risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented **S22**: SRR: addition of information regarding meningiomas in alignment with the CDS.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors.

• Sulfbromophthalein and other liver function test values may be increased slightly.

There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – [Return of ovulation](#).

Use in pregnancy – Pregnancy Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM injection of 150-mg MPA may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on MPA [Injection 150 mg IM](#) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with MPA injection 150 mg IM, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

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Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

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Table 3. Events associated with the use of SC MPA for endometriosis-associated pain-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations

MedDRA SOC	Event
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

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As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous(SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

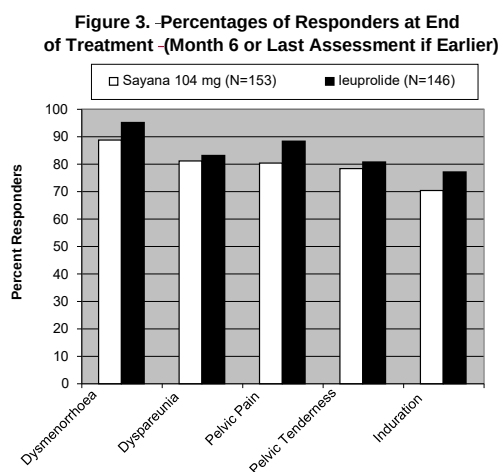
In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomized, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months -or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

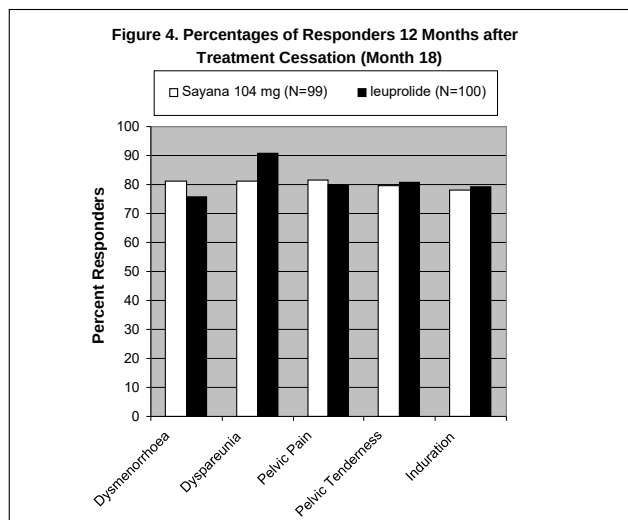
The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SAYANA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SAYANA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using DEPO-PROVERA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception.

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SAYANA women became pregnant while one of the DEPO-PROVERA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6: Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from depot medroxyprogesterone acetate (DMPA) use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42).

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pre-filled syringe contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

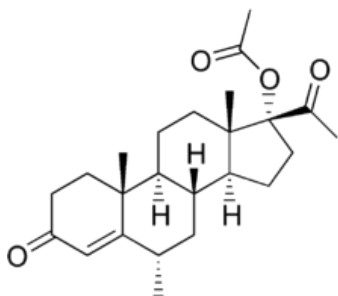
SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: ~~6~~ α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: ~~C~~ $C_{24}H_{34}O_4$.

Molecular weight: ~~3~~386.5.

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

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9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

~~20 April 2023~~ [DD Month YYYY](#)

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Summary Table of Changes

Section changed	Summary of new information
4.8	~~Addition of 'injection site discolouration' as post-marketing ADR~~
6.1	~~Update to the AAN of the excipient, monobasic sodium phosphate monohydrate~~
8	~~Update to sponsor website address~~
4.4	Addition of information regarding meningioma
All	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION – SAYANA® PRESS (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS 104 mg/0.65 mL suspension for injection ampoule with attached needle (pre-filled injector) contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA PRESS contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA PRESS is supplied as a single dose ampoule with attached needle (pre-filled injector) containing 104 mg MPA in 0.65 mL suspension for injection. SAYANA PRESS is a white to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18-years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA PRESS must be given by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA PRESS is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA PRESS (104 mg) is given. Dosage does not need to be adjusted for body weight.

Method of administration

SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional. If self-administration is planned, the healthcare professional should make an assessment of the patient's skill and competence with the procedure. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate. While on self-injection treatment, it is recommended that the patient visit their doctor at periodic intervals.

Mixing the medicine

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: SAYANA PRESS ampoule with attached needle (pre-filled injector), alcohol swabs and cotton pads.

Each SAYANA PRESS pre-filled injector contains a white to off-white homogeneous suspension. The contents are completely sealed inside the reservoir of the pre-filled injector. As with other parenteral drug products, SAYANA PRESS should be inspected visually for particulate matter and discolouration prior to administration. The pre-filled injector of SAYANA PRESS must be vigorously shaken for at least 30 seconds just before use to create a uniform suspension.

Activating the SAYANA PRESS pre-filled injector

The pre-filled injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid.

Administration

The dose is administered as a SC injection into the anterior thigh or abdomen. When the injection is being given, the pre-filled injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

For full instructions, see Instructions for Use sheet provided with each pack of SAYANA PRESS.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA PRESS should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA PRESS injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA PRESS within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA PRESS, contraceptive coverage will be maintained provided the first SAYANA PRESS injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA PRESS is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties – Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA PRESS is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use**Route of administration**

SAYANA PRESS is not formulated for IM injection. SAYANA PRESS must be given by SC injection.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SC MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical Trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1: Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with IM MPA 150 mg and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1: Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies.

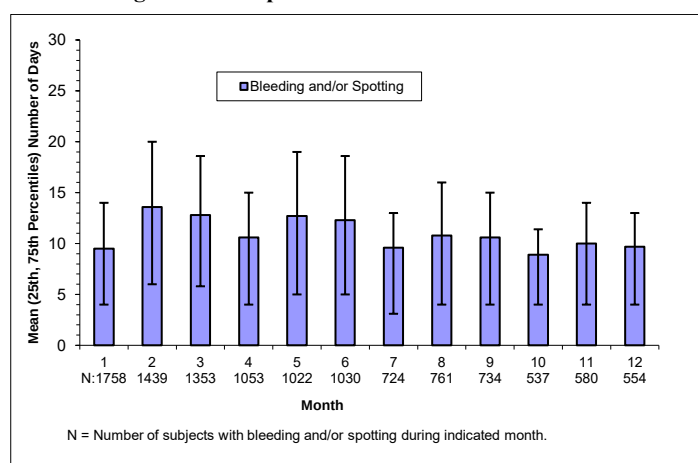
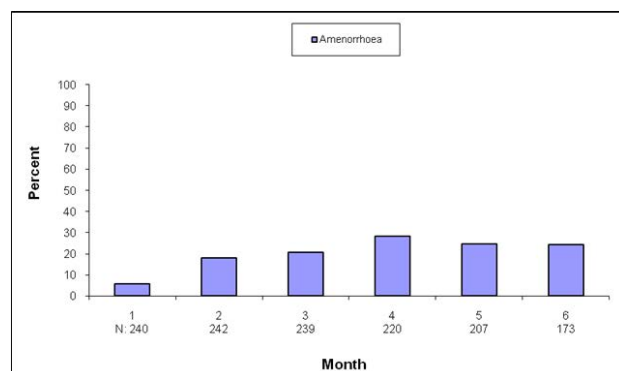


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289).



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of IM MPA injection (150 mg) use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A ~~R~~relative ~~R~~risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented 22 SRR: addition of information regarding meningiomas in alignment with the CDS.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the

maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that SC MPA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SC MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA PRESS is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA PRESS is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA PRESS by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical

trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors.

•Sulfbromophthalein and other liver function test values may be increased slightly.

There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA PRESS.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA PRESS users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – •Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA PRESS is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA PRESS is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM MPA injection (150 mg) may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on IM MPA injection (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with IM MPA injection (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA PRESS has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception.

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia

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MedDRA SOC	Event
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

SC MPA: subcutaneous medroxyprogesterone acetate

$\% = (n/\text{Total Reported}) * 100$, ++ Version 2.3 of the MedDRA Dictionary was used.
Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA PRESS suspension for subcutaneous (SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

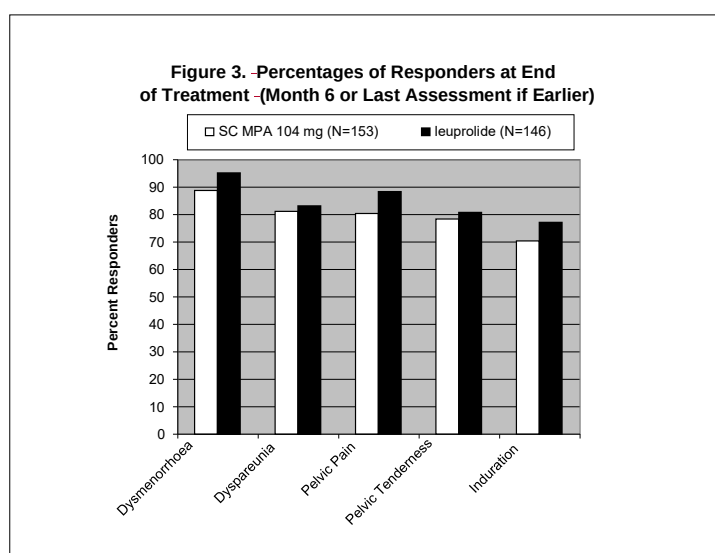
Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent

symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SC MPA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SC MPA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).

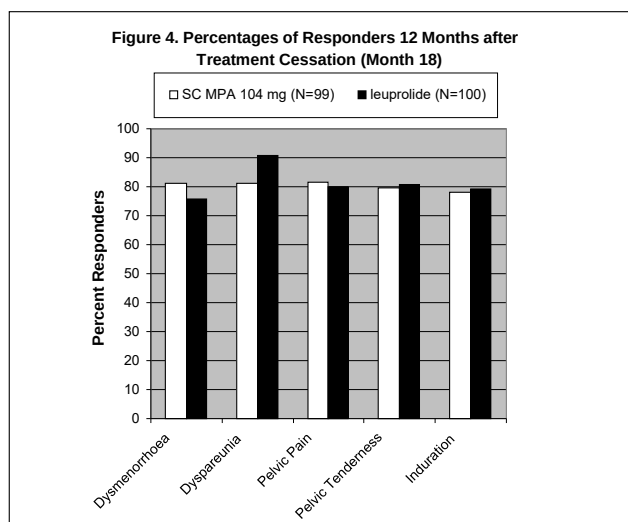


A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No

pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using IM MPA injection (150 mg) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of IM MPA injection (150 mg), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using IM MPA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5: Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception.

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SC MPA women became pregnant while one of the IM MPA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6: Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy.

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of IM MPA injection (150 mg) every 3 months for up to 240 weeks [4.6 years] in adolescent females (12–18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was

discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from IM MPA use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7: Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42):

	C _{max} (ng/mL)	T _{max} (day)	C _{91 (min)} (ng/mL)	AUC ₀₋₉₁ (ng·day/mL)	AUC _{0-∞} (ng·day/mL)	t _{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration.

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the $C_{\min}$ and the SC dose of MPA appeared to be linear. The mean $C_{\max}$ did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of MPA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women ($n=42$, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA $C_{\max}$ was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough ($C_{\min}$) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ampoule with attached needle (pre-filled injector) contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. -Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA PRESS 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose ampoule with attached needle (pre-filled injector).

The product containing part of the pre-filled injector is made of linear low density polyethylene laminate with a siliconised stainless steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

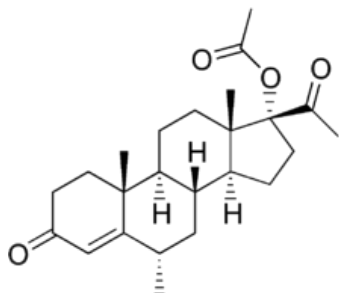
6.6 Special precautions for disposal

A puncture-resistant container should be used. If the product is self-administered, the patient should be told of the importance of proper pre-filled injector and needle disposal and be cautioned against reuse of these items.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: ~~C₂₄H₃₄O₄~~

Molecular weight: ~~386.5~~

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

Commented [S22]: MEC: update to the website details of the same site

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

~~09 August 2023~~ DD Month YYYY

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
All	Change in trade name.
4.2, 6.5	Changes to container from pre-filled glass syringe to ampoule with attached needle (pre-filled injector). Addition of Instructions for Use for pre-filled injector.
6.4	Change in storage conditions
6.6	Addition of recommendation of pre-filled injector disposal
4.4	Addition of information regarding meningioma
All	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION –
PROVERA® (MEDROXYPROGESTERONE
ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

Commented s22 : MEC: Add acronym of
medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablets contain 2.5 mg, 5 mg, 10 mg, 100 mg, 200 mg, 250 mg or 500 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect:

Lactose monohydrate (2.5, 5 and 10 mg tablets)

Sodium benzoate (100, 200, 250 and 500 mg tablets)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

100 mg tablets: white, scored, marked U467.

200 mg tablets: white, scored, marked U320.

250 mg tablets: white, scored, marked U403.

500 mg tablets: white, capsule-shaped, marked UPJOHN 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with [MPA](#) ~~medroxyprogesterone acetate~~.

Commented [s22](#) : Minor editorial change

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use**Physical examination**

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented s22 : SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine

and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use PROVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

PROVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should

consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of PROVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the

control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5, 5, and 10 mg tablets:

calcium stearate
indigo carmine (5 mg tablet)
sunset yellow FCF (2.5 mg tablet)
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose

PROVERA 100, 200, 250, and 500 mg tablets:

docusate sodium
gelatin
isopropyl alcohol
macrogol 400
magnesium stearate
maize starch
microcrystalline cellulose
purified water
sodium benzoate
sodium starch glycollate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PROVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

100 mg tablets: blister packs of 10 and 100 tablets.

200 mg tablets: blister packs of 10 and 60 tablets.

250 mg tablets: blister packs of 10 and 60 tablets.

500 mg tablets: blister packs of 10, 30 and 60 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

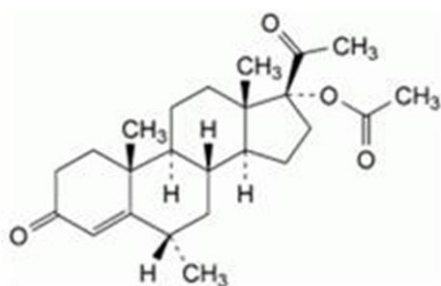
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

10. DATE OF REVISION

~~29 April 2020~~: [DD Month YYYY](#)

® Registered trademark.

Commented [s22] : Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CML.

Summary Table of Changes

Section changed	Summary of new information
All	New PI reformat and editorial changes
4.4 and 5.1	Amend BMD recovery time in adolescent females
8	Sponsor address updated
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION –
RALOVERA[®] (MEDROXYPROGESTERONE
ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

Commented s22 : MEC: Add acronym of medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RALOVERA tablets contain 2.5 mg, 5 mg or 10 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect:

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with ~~medroxyprogesterone acetate~~ MPA.

Commented s22 : Minor editorial change

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy (HRT) should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

RALOVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with RALOVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented S22 : SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of

several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of HRT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of RALOVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use RALOVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of RALOVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of RALOVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

RALOVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than

70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test – the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with RALOVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

RALOVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on RALOVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdose, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of RALOVERA.

However, ~~In~~ a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from

baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and total hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

RALOVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium stearate
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose
sunset yellow FCF (2.5 mg tablet)
indigo carmine (5 mg tablet)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

RALOVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

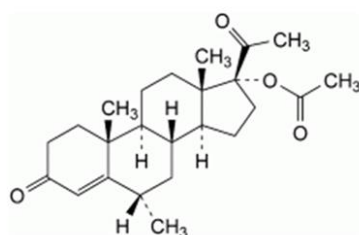
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 October 1993-

Commented s22 : Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CMI.

10. DATE OF REVISION

~~29 April 2020~~.[DD Month YYYY](#)

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
~~All~~	~~New PI reformat and editorial changes~~
~~4.4 and 5.1~~	~~Amend BMD recovery time in adolescent females~~
~~8~~	~~Sponsor address updated~~
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-PROVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use MPA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-PROVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By Month 12, amenorrhoea was reported by 57% of

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).

DEPO-PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-PROVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO PROVERA may significantly decrease the serum concentration of MPA. DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on

MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use – Return of fertility.

Use in pregnancy – Pregnancy Category D

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. In mothers who are breastfeeding and who are treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

- *Cardiac disorders:* Palpitations, myocardial infarction, congestive heart failure.
- *Endocrine disorders:* Prolonged anovulation, Cushingoid syndrome.
- *Eye disorders:* Retinal embolism and thrombosis, diabetic cataract, visual impairment.
- *Gastrointestinal:* Abdominal distension, nausea, constipation, diarrhoea, dry mouth.
- *General disorders and administrative site conditions:* Fatigue, injection site reactions, malaise, hyperpyrexia.
- *Hepatobiliary disorders:* Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
- *Immune system disorders:* Anaphylactic reactions, anaphylactoid reactions, angioedema.
- *Investigations:* Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.
- *Metabolic and nutritional disorders:* Exacerbation of diabetes mellitus, hypercalcaemia.
- *Musculoskeletal and connective tissue disorders:* Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.
- *Nervous System disorders:* Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.
- *Psychiatric disorders:* Depression, insomnia, nervousness.
- *Renal and urinary system disorders:* Glycosuria.
- *Reproductive and breast disorders:* Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

- *Respiratory, thoracic and mediastinal disorders:* Pulmonary embolism.
- *Skin and subcutaneous tissue disorders:* Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.
- *Vascular disorders:* Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

- *Blood and lymphatic system disorders:* Blood dyscrasia, anaemia.

- Cardiac disorders: Tachycardia, chest pain.
- Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.
- General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.
- Hepatobiliary disorders: Jaundice, jaundice cholestatic.
- Immune systems disorders: Drug hypersensitivity reactions.
- Metabolism and nutrition disorders: Changes in appetite.
- Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.
- Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.
- Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.
- Renal and urinary disorders: Genitourinary infections.
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.
- Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.
- Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.
- Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD

was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial.
- 1 x 1 mL pre-filled syringe.

Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

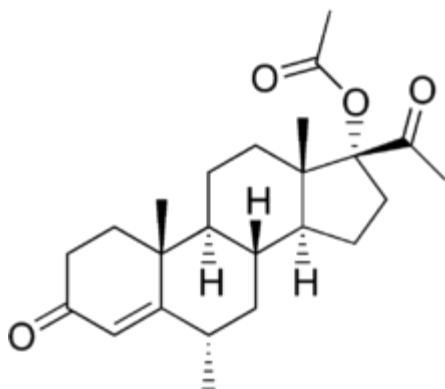
6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in

chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma

	Minor editorial changes
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – DEPO-RALOVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By Month 12, amenorrhoea was reported by 57% of

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-RALOVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-RALOVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when DEPO-RALOVERA is used long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-RALOVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-RALOVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-RALOVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated

with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-RALOVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-RALOVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-RALOVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-RALOVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-RALOVERA. Therefore, if such tests are abnormal in a patient taking DEPO-RALOVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-RALOVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA. DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use - Return of fertility

Use in pregnancy – Pregnancy Category D

DEPO-RALOVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-RALOVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-RALOVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-RALOVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating

- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events reported by fewer than 1% of subjects:

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobiliary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular

maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

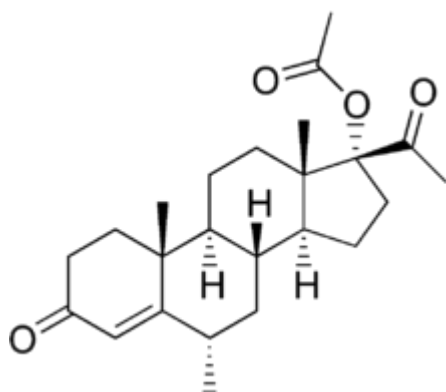
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

31 May 1993

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] PRESS (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS 104 mg/0.65 mL suspension for injection ampoule with attached needle (pre-filled injector) contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA PRESS contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA PRESS is supplied as a single dose ampoule with attached needle (pre-filled injector) containing 104 mg MPA in 0.65 mL suspension for injection. SAYANA PRESS is a white to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA PRESS must be given by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA PRESS is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA PRESS (104 mg) is given. Dosage does not need to be adjusted for body weight.

Method of administration

SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional. If self-administration is planned, the healthcare professional should make an assessment of the patient's skill and competence with the procedure. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate. While on self-injection treatment, it is recommended that the patient visit their doctor at periodic intervals.

Mixing the medicine

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: SAYANA PRESS ampoule with attached needle (pre-filled injector), alcohol swabs and cotton pads.

Each SAYANA PRESS pre-filled injector contains a white to off-white homogeneous suspension. The contents are completely sealed inside the reservoir of the pre-filled injector. As with other parenteral drug products, SAYANA PRESS should be inspected visually for particulate matter and discolouration prior to administration. The pre-filled injector of SAYANA PRESS must be vigorously shaken for at least 30 seconds just before use to create a uniform suspension.

Activating the SAYANA PRESS pre-filled injector

The pre-filled injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid.

Administration

The dose is administered as a SC injection into the anterior thigh or abdomen. When the injection is being given, the pre-filled injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

For full instructions, see Instructions for Use sheet provided with each pack of SAYANA PRESS.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA PRESS should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA PRESS injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA PRESS within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA PRESS, contraceptive coverage will be maintained provided the first SAYANA PRESS injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA PRESS is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties - Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA PRESS is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use**Route of administration**

SAYANA PRESS is not formulated for IM injection. SAYANA PRESS must be given by SC injection.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SC MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1. Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with IM MPA 150 mg and after 2 years post-therapy or 7 years of observation (control)

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1. Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies

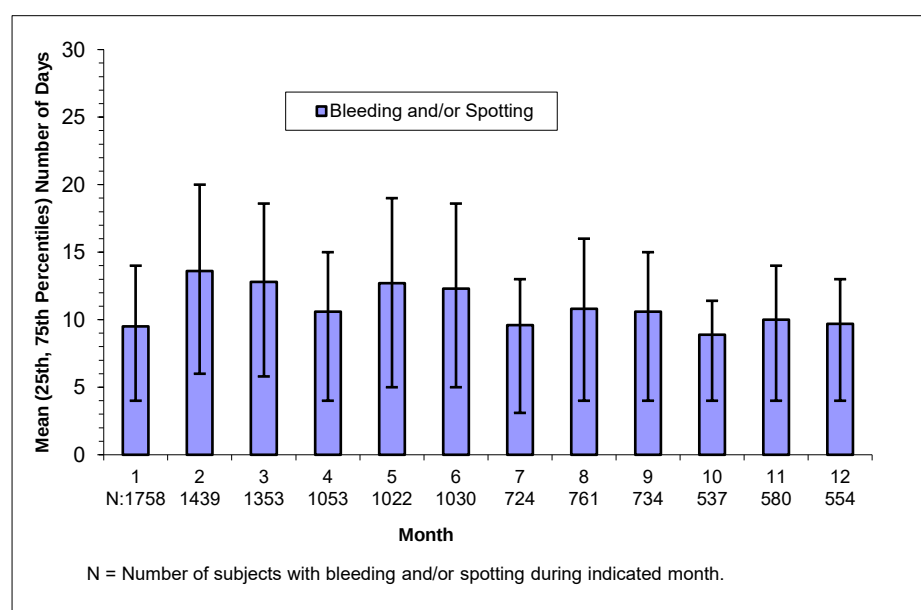
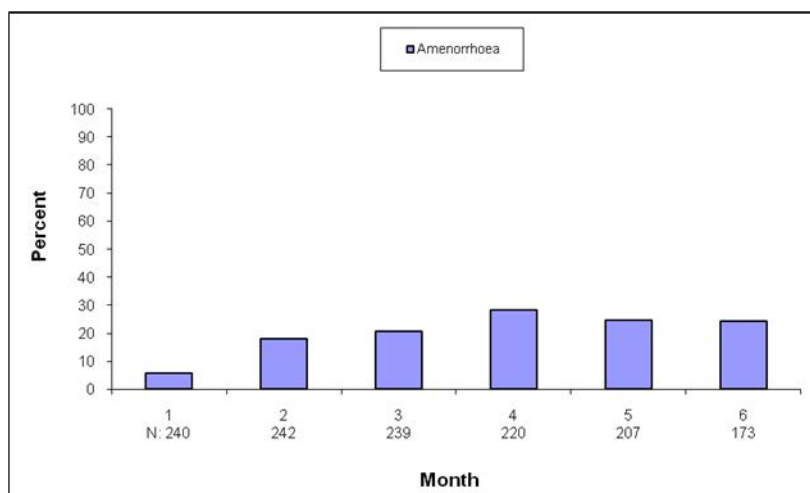


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289)



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of IM MPA injection (150 mg) use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A relative risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the

maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that SC MPA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SC MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA PRESS is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA PRESS is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA PRESS by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical

trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors. Sulfobromophthalein and other liver function test values may be increased slightly. There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA PRESS.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA PRESS users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA PRESS is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA PRESS is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM MPA injection (150 mg) may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on IM MPA injection (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with IM MPA injection (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA PRESS has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia

MedDRA SOC	Event
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

SC MPA: subcutaneous medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infarction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA PRESS suspension for subcutaneous (SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

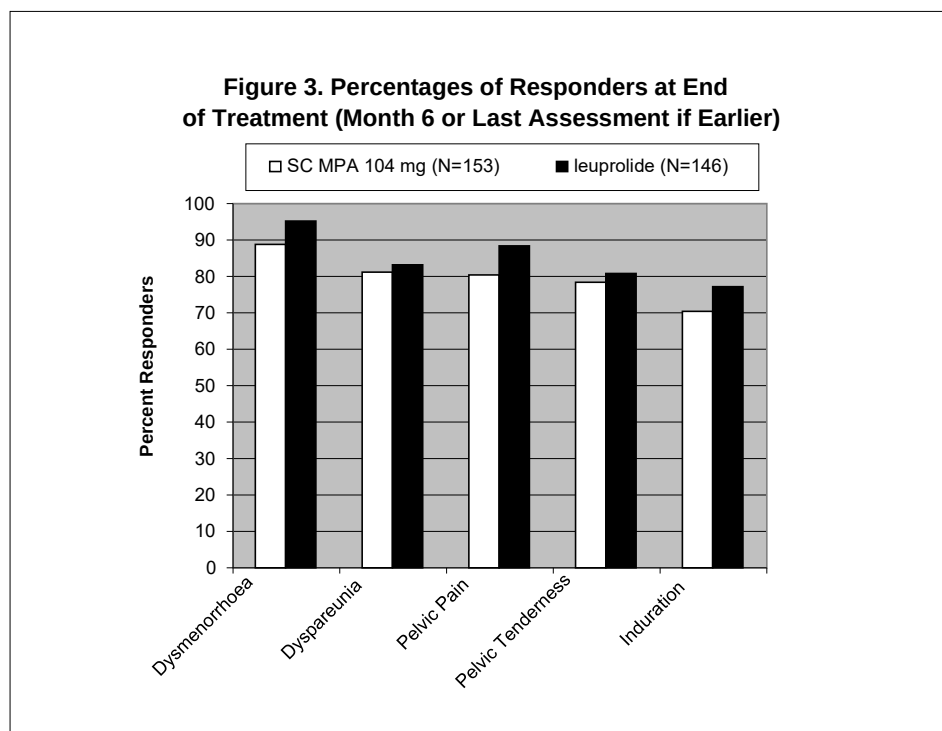
Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SC MPA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide

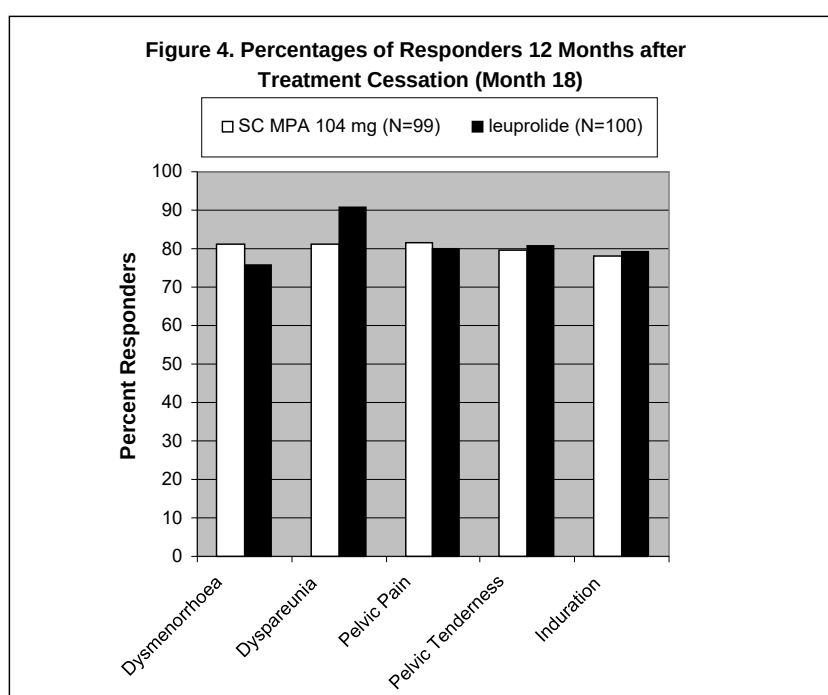
versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SC MPA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using IM MPA injection (150 mg) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of IM MPA injection (150 mg), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using IM MPA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SC MPA women became pregnant while one of the IM MPA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of IM MPA injection (150 mg) every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from IM MPA use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of MPA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ampoule with attached needle (pre-filled injector) contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA PRESS 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose ampoule with attached needle (pre-filled injector).

The product containing part of the pre-filled injector is made of linear low density polyethylene laminate with a siliconised stainless steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

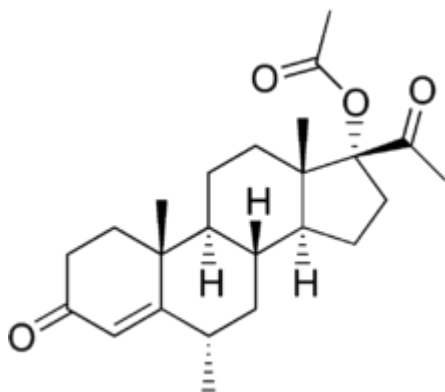
6.6 Special precautions for disposal

A puncture-resistant container should be used. If the product is self-administered, the patient should be told of the importance of proper pre-filled injector and needle disposal and be cautioned against reuse of these items.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: C₂₄H₃₄O₄

Molecular weight: 386.5

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

DD Month YYYY

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
All	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA 104 mg/0.65 mL suspension for injection syringe contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg MPA in 0.65 mL suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA must be given by subcutaneous injection (SC MPA) into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: pre-filled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties - Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use

Route of administration

SAYANA is not formulated for IM injection. SAYANA must be given by SC injection.

Physical examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control

group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1. Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with MPA 150 mg IM and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received MPA injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received MPA Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1. Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies

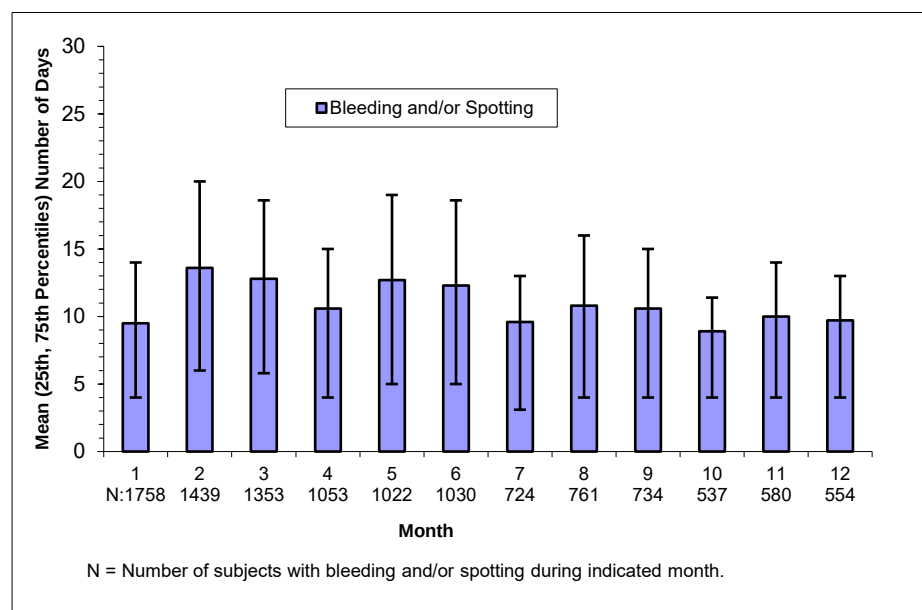
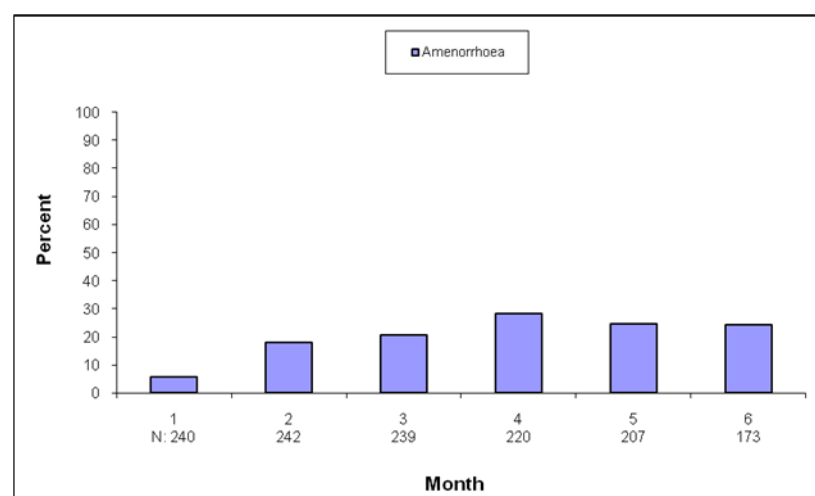


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289)



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of depot MPA IM 150 mg use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the

previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A relative risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors. Sulfobromophthalein and other liver function test values may be increased slightly. There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM injection of 150 mg MPA may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on MPA injection 150 mg IM are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with MPA injection 150 mg IM, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk

have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia

MedDRA SOC	Event
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous(SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was

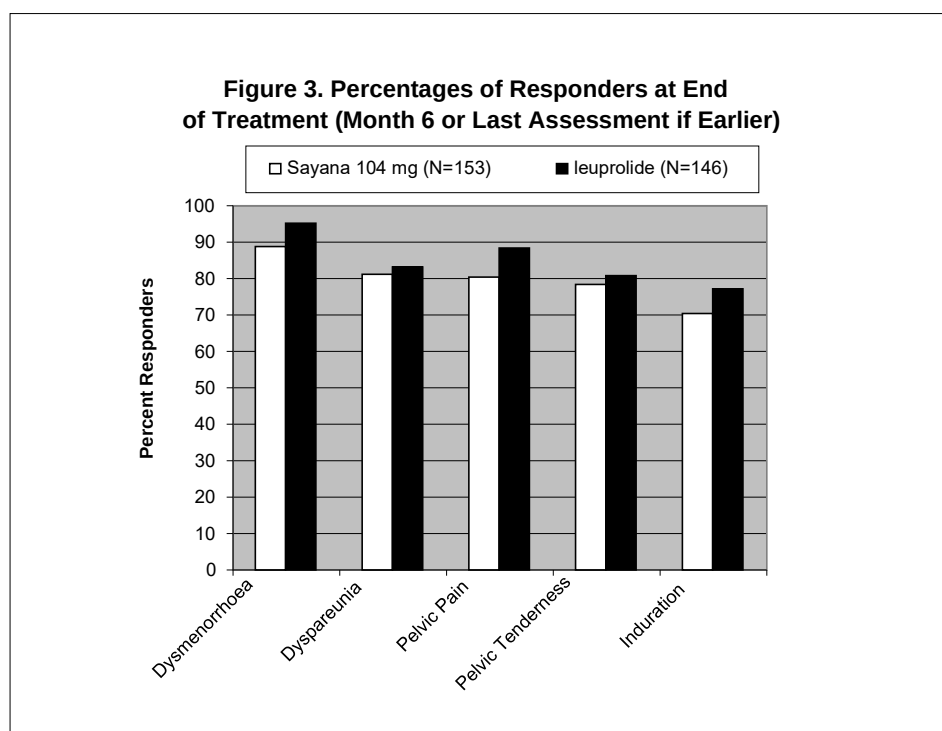
not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

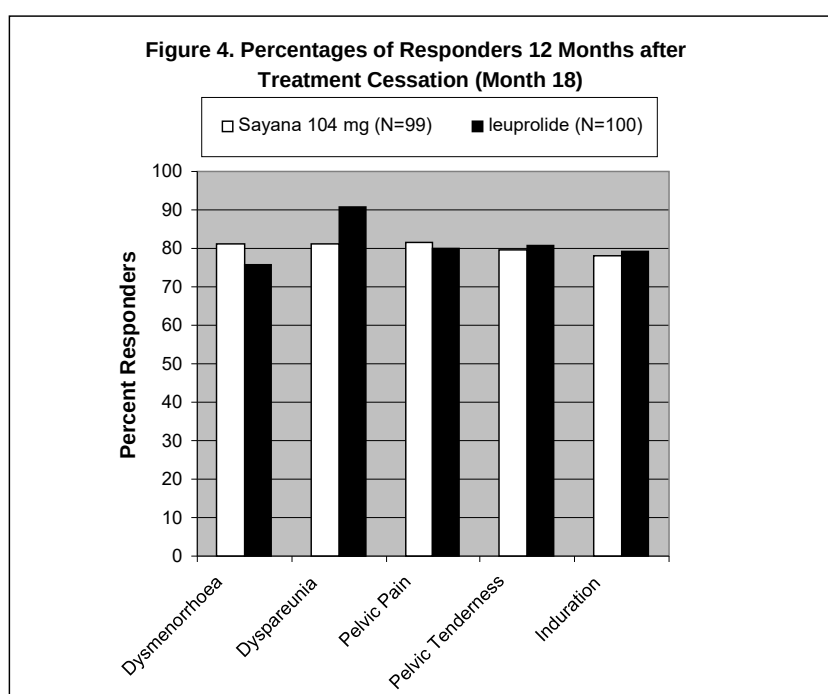
The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SAYANA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SAYANA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using DEPO-PROVERA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SAYANA women became pregnant while one of the DEPO-PROVERA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from depot medroxyprogesterone acetate (DMPA) use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the $C_{\min}$ and the SC dose of MPA appeared to be linear. The mean $C_{\max}$ did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA $C_{\max}$ was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough ($C_{\min}$) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pre-filled syringe contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

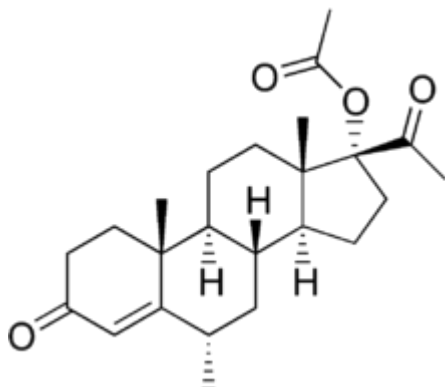
SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate

Molecular formula: C₂₄H₃₄O₄

Molecular weight: 386.5.

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

DD Month YYYY

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Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
All	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – PROVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablets contain 2.5 mg, 5 mg, 10 mg, 100 mg, 200 mg, 250 mg or 500 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect

Lactose monohydrate (2.5, 5 and 10 mg tablets)

Sodium benzoate (100, 200, 250 and 500 mg tablets)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

100 mg tablets: white, scored, marked U467.

200 mg tablets: white, scored, marked U320.

250 mg tablets: white, scored, marked U403.

500 mg tablets: white, capsule-shaped, marked UPJOHN 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with MPA.

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use**Physical examination**

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine

and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use PROVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

PROVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should

consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of PROVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the

control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5, 5, and 10 mg tablets:

calcium stearate
indigo carmine (5 mg tablet)
sunset yellow FCF (2.5 mg tablet)
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose

PROVERA 100, 200, 250, and 500 mg tablets:

docusate sodium
gelatin
isopropyl alcohol
macrogol 400
magnesium stearate
maize starch
microcrystalline cellulose
purified water
sodium benzoate
sodium starch glycollate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PROVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

100 mg tablets: blister packs of 10 and 100 tablets.

200 mg tablets: blister packs of 10 and 60 tablets.

250 mg tablets: blister packs of 10 and 60 tablets.

500 mg tablets: blister packs of 10, 30 and 60 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

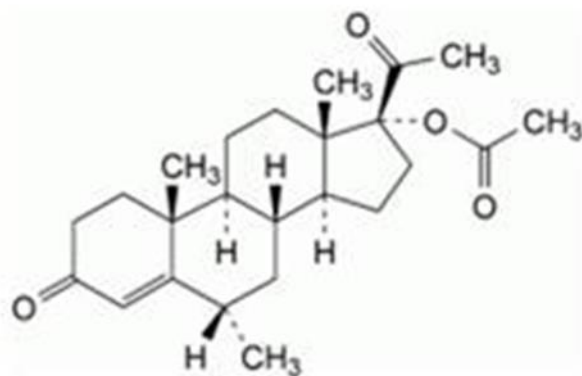
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

10. DATE OF REVISION

DD Month YYYY

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
1, 4.1	Minor editorial changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – RALOVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RALOVERA tablets contain 2.5 mg, 5 mg or 10 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with MPA.

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy (HRT) should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

RALOVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with RALOVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of

several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of HRT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of RALOVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use RALOVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of RALOVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of RALOVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

RALOVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than

70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test – the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with RALOVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

RALOVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on RALOVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdose, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of RALOVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from

baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and total hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

RALOVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium stearate
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose
sunset yellow FCF (2.5 mg tablet)
indigo carmine (5 mg tablet)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

RALOVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

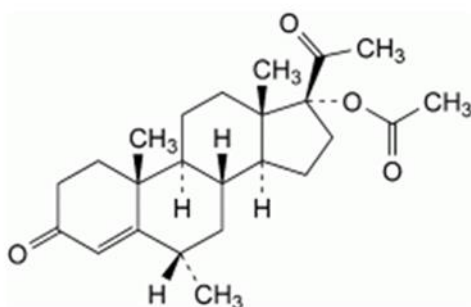
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 October 1993

10. DATE OF REVISION

DD Month YYYY

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address



Australian Government
Department of Health and Aged Care
 Therapeutic Goods Administration

The Managing Director
 Pfizer Australia Pty Ltd

Clinical File: 2014/040108
 PI File: 2015/003991
 Submission No.: PM-2024-00437-1-4
 Data: [e001209 \(0041-\)](#)

Attention:

s22
s22 @pfizer.com

Dear Sir/Madam,

REQUEST UNDER s. 9D(2) FOR SAFETY-RELATED VARIATION TO THE ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

REQUEST UNDER s. 9D(3) FOR VARIATION TO THE ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

I refer to your request under subsections 9D(2) and 9D(3) of the *Therapeutic Goods Act 1989* (the Act) dated 6 February 2024 to vary the entry of:

- 12300 - DEPO-PROVERA medroxyprogesterone acetate 150 mg/mL aqueous suspension injection vial
- 12331 - PROVERA medroxyprogesterone acetate 100mg tablet blister pack
- 12333 - PROVERA medroxyprogesterone acetate 200mg tablet blister pack
- 12334 - PROVERA medroxyprogesterone acetate 250mg tablet blister pack
- 12336 - PROVERA medroxyprogesterone acetate 500mg tablet blister pack
- 167889 - SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe
- 401610 - DEPO-PROVERA medroxyprogesterone acetate 150 mg/1 mL suspension for injection pre-filled syringe
- 401897 - SAYANA PRESS medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection ampoule with attached needle
- 42932 - PROVERA Medroxyprogesterone acetate 2.5mg tablet blister pack
- 42933 - PROVERA Medroxyprogesterone acetate 5mg tablet blister pack (New Formula)
- 42934 - PROVERA Medroxyprogesterone acetate 10mg tablet blister pack (new embossing)
- 42935 - PROVERA Medroxyprogesterone acetate 10mg tablet bottle (new embossing)
- 44464 - DEPO-RALOVERA medroxyprogesterone acetate 150 mg/1 mL injection vial
- 46527 - RALOVERA medroxyprogesterone acetate 2.5mg tablet blister pack
- 46531 - RALOVERA medroxyprogesterone acetate 5mg tablet blister pack
- 46532 - RALOVERA medroxyprogesterone acetate 10mg tablet blister pack
- 46534 - RALOVERA medroxyprogesterone acetate 10mg tablet bottle

(referred to hereinafter as the product(s)) in the Australian Register of Therapeutic Goods (the ARTG) as described in **Attachment 2a**.

Approval of such a request would result in a decision by the Secretary under subsection 25AA(4) to reflect any variation made under subsection 9D(2) and 9D(3).

Subsections 9D(2), 9D(3), 25AA(4) of the Act can be found online at the following link:
<https://www.legislation.gov.au/Series/C2004A03952>

Decision

As delegate of the Secretary of the Department of Health and Aged Care, I am:

- under subsection 9D(2) and 9D(3) of the Act, varying the information in the entry of the product(s) in the ARTG as requested
- under subsection 25AA(4) of the Act, approving the text of the approved Product Information (PI) for the product(s) to reflect this as set out in the version at **Attachment 2a and 2b** on the basis that the only changes made to the most recently approved PI were those set out in your request of 6 February 2024. This approval is based on the evaluation of the information provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Date of effect

The date of effect of the variation is the date of this approval letter. The “Date of revision” included in the PI is to be the date of this letter.

Action required of you

The approved PI at **Attachment 2b** must be lodged with the TGA **within 2 weeks** of the date of approval of the variation. If the related Consumer Medicine Information (CMI) document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA **within 2 weeks** of the date of the changed PI.

The documents must be lodged in the TGA eBusiness Services system. Information on how to lodge these documents is available at www.ebs.tga.gov.au. The documents must be in text PDF format – scanned PDF documents will **not** be accepted by the system.

Review rights

Details of review rights for the decision under subsection 9D(2), 9D(3) and 25AA(4) are provided at **Attachment 1**.

Your obligations in relation to Product Information etc.

You are reminded that an approved PI for a medicine cannot be changed without the approval of the Secretary under subsection 25AA(4) of the Act.

You are also reminded that the Consumer Medicine Information must comply with the requirements set out in the Therapeutic Goods Regulations 1990, which includes the obligation to ensure the CMI that must be supplied with the medicine is ‘consistent with’ the approved PI.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully,

Electronically signed and authorised by

s22

Delegate of the Secretary

Pharmacist Evaluation Section

Prescription Medicines Authorisation Branch

Email: s22@health.gov.au

26 February 2024

Attachments:

1. Review rights
2. Approved product information for:
 - a. DEPO-PROVERA/DEPO-RALOVERA/SAYANA/SAYANA PRESS
medroxyprogesterone acetate injection (changes highlighted)
PROVERA/RALOVERA medroxyprogesterone acetate tablet (changes highlighted)
 - b. DEPO-PROVERA/DEPO-RALOVERA/SAYANA/SAYANA PRESS
medroxyprogesterone acetate injection (clean)
PROVERA/RALOVERA medroxyprogesterone acetate tablet (clean)

Attachment 1**Request for reconsideration of an initial decision**

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: **'decision.review@health.gov.au'**

Subject: **"<insert name of person/company making request> - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989*"**

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "... - Email 1 of 3", "... - Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of the Act, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-PROVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use MPA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented **S22** : SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or

is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-PROVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By ~~at~~Month 12, amenorrhoea was reported by 57% of women, and by ~~at~~Month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).

DEPO-PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or -corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease

- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-PROVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO PROVERA may significantly decrease the serum concentration of MPA. -DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use – Return of fertility.

Use in pregnancy – Pregnancy Category D

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. In mothers who are breastfeeding and who are treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

- *Cardiac disorders:* Palpitations, myocardial infarction, congestive heart failure.
- *Endocrine disorders:* Prolonged anovulation, Cushingoid syndrome.
- *Eye disorders:* Retinal embolism and thrombosis, diabetic cataract, visual impairment.
- *Gastrointestinal:* Abdominal distension, nausea, constipation, diarrhoea, dry mouth.
- *General disorders and administrative site conditions:* Fatigue, injection site reactions, malaise, hyperpyrexia.
- *Hepatobiliary disorders:* Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
- *Immune system disorders:* Anaphylactic reactions, anaphylactoid reactions, angioedema.
- *Investigations:* Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.
- *Metabolic and nutritional disorders:* Exacerbation of diabetes mellitus, hypercalcaemia.
- *Musculoskeletal and connective tissue disorders:* Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

- *Nervous System disorders:* Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.
- *Psychiatric disorders:* Depression, insomnia, nervousness.
- *Renal and urinary system disorders:* Glycosuria.
- *Reproductive and breast disorders:* Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary embolism.
- *Skin and subcutaneous tissue disorders:* Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.
- *Vascular disorders:* Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash

- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

- Blood and lymphatic system disorders: Blood dyscrasia, anaemia.
- Cardiac disorders: Tachycardia, chest pain.
- Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.
- General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.
- Hepatobiliary disorders: Jaundice, jaundice cholestatic.
- Immune systems disorders: Drug hypersensitivity reactions.
- Metabolism and nutrition disorders: Changes in appetite.
- Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.
- Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.
- Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.
- Renal and urinary disorders: Genitourinary infections.
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.
- Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.
- Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.
- Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial.
- 1 x 1 mL pre-filled syringe.

Not all presentations may be marketed.

6.6 Special precautions for disposal

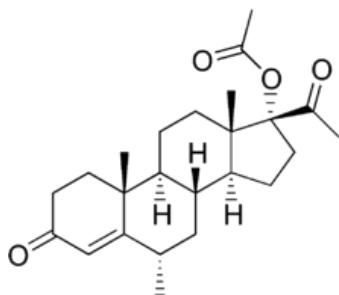
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

Commented [522]: Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CMI.

10. DATE OF REVISION

03 May 2023DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
~~6.4~~	~~Updated special precautions for storage, ‘Do not refrigerate or freeze’.~~
~~6.5~~	~~Updated description for the pre-filled syringe presentation and information on marketed presentations.~~
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – DEPO-RALOVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented **S22** : SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or

is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By ~~at~~Month 12, amenorrhoea was reported by 57% of women, and by ~~at~~Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-RALOVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-RALOVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated ~~when~~ DEPO-RALOVERA is used long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-RALOVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or -corticosteroids

Commented ~~S22~~ : Minor editorial change

- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-RALOVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-RALOVERA in women who were first exposed before the

age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-RALOVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes

should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-RALOVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-RALOVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-RALOVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-RALOVERA. Therefore, if such tests are abnormal in a patient taking DEPO-RALOVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-RALOVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased

- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA. -DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use - Return of fertility

Use in pregnancy – Pregnancy Category D

DEPO-RALOVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-RALOVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-RALOVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period

- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-RALOVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression

- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events reported by fewer than 1% of subjects:

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobiliary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

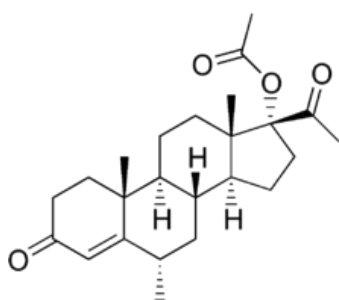
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

Commented s22 : Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CML.

9. DATE OF FIRST APPROVAL

31 May 1993-

10. DATE OF REVISION

~~27 April 2023~~[DD Month YYYY](#)

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
~~Throughout~~	~~Minor editorial changes~~
~~6.4~~	~~Updated special precautions for storage, ‘Do not refrigerate or freeze’.~~
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – SAYANA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA 104 mg/0.65 mL suspension for injection syringe contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

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Excipient(s) with known effect

SAYANA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg MPA in 0.65 mL suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra indicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA must be given by subcutaneous injection (SC MPA) into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). SAYANA is not formulated for intramuscular (IM) injection.

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It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: pre-filled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from ~~intramuscular (IM) MPA~~ MPA (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for IM MPA (150 mg).

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BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties – Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment

Renal impairment

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use

Route of administration

SAYANA is not formulated for IM injection. SAYANA must be given by SC injection.

Physical examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical Trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control

group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86% , -4.11% , -4.89% , -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1: Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with MPA 150 mg IM and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received MPA injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received MPA Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during ~~the~~Month 6 and 56.5% experienced amenorrhoea during ~~the~~Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

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Figure 1: Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies.

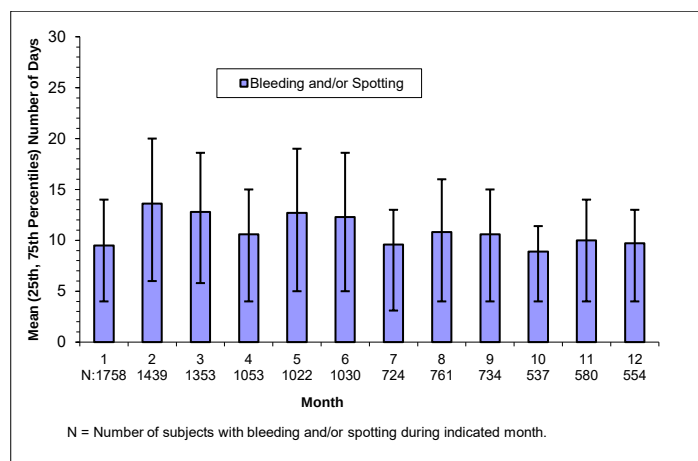
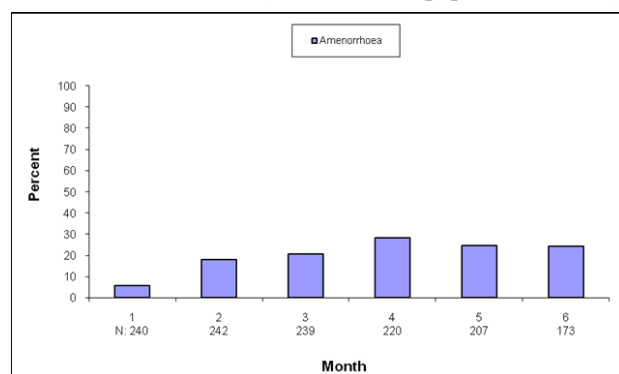


Figure 2: Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289).



Cancer risks

Long-term case-controlled surveillance of depot MPA IM 150 mg use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the

previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A ~~R~~relative ~~R~~risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented **S22**: SRR: addition of information regarding meningiomas in alignment with the CDS.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors.

sulfobromophthalein and other liver function test values may be increased slightly.

There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – [Return of ovulation](#).

Use in pregnancy – Pregnancy Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM injection of 150-mg MPA may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on MPA [Injection 150 mg IM](#) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with MPA injection 150 mg IM, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

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Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

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Table 3. Events associated with the use of SC MPA for endometriosis-associated pain-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations

MedDRA SOC	Event
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

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As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous(SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

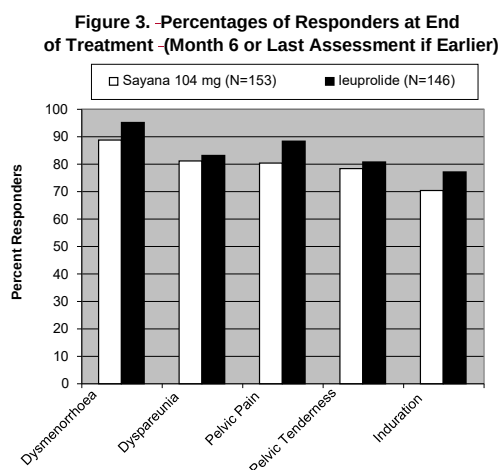
In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomized, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months -or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

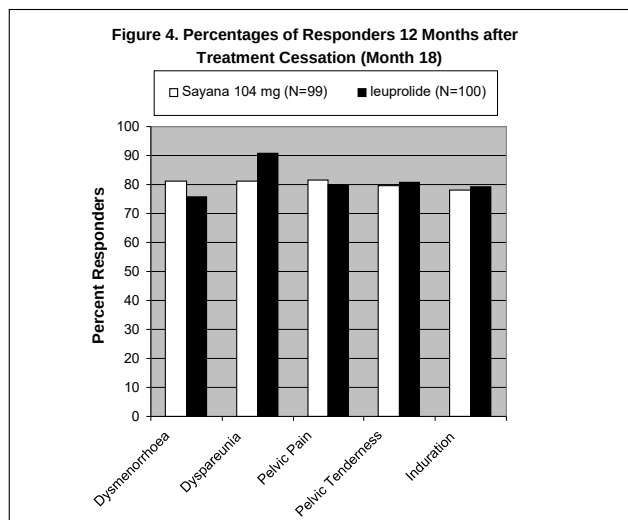
The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SAYANA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SAYANA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using DEPO-PROVERA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception.

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SAYANA women became pregnant while one of the DEPO-PROVERA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6: Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from depot medroxyprogesterone acetate (DMPA) use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42).

	C _{max} (ng/mL)	T _{max} (day)	C _{91 (min)} (ng/mL)	AUC ₀₋₉₁ (ng·day/mL)	AUC _{0-∞} (ng·day/mL)	t _{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pre-filled syringe contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

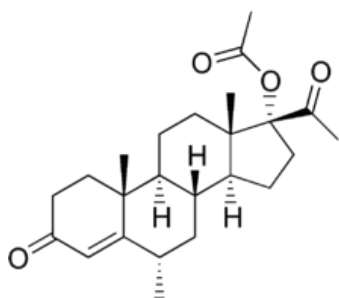
SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: ~~6~~ α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: ~~C~~ $C_{24}H_{34}O_4$.

Molecular weight: ~~3~~386.5.

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

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9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

~~20 April 2023~~ [DD Month YYYY](#)

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Summary Table of Changes

Section changed	Summary of new information
4.8	~~Addition of 'injection site discolouration' as post-marketing ADR~~
6.1	~~Update to the AAN of the excipient, monobasic sodium phosphate monohydrate~~
8	~~Update to sponsor website address~~
4.4	Addition of information regarding meningioma
All	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION – SAYANA® PRESS (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS 104 mg/0.65 mL suspension for injection ampoule with attached needle (pre-filled injector) contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA PRESS contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA PRESS is supplied as a single dose ampoule with attached needle (pre-filled injector) containing 104 mg MPA in 0.65 mL suspension for injection. SAYANA PRESS is a white to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18-years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA PRESS must be given by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA PRESS is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA PRESS (104 mg) is given. Dosage does not need to be adjusted for body weight.

Method of administration

SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional. If self-administration is planned, the healthcare professional should make an assessment of the patient's skill and competence with the procedure. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate. While on self-injection treatment, it is recommended that the patient visit their doctor at periodic intervals.

Mixing the medicine

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: SAYANA PRESS ampoule with attached needle (pre-filled injector), alcohol swabs and cotton pads.

Each SAYANA PRESS pre-filled injector contains a white to off-white homogeneous suspension. The contents are completely sealed inside the reservoir of the pre-filled injector. As with other parenteral drug products, SAYANA PRESS should be inspected visually for particulate matter and discolouration prior to administration. The pre-filled injector of SAYANA PRESS must be vigorously shaken for at least 30 seconds just before use to create a uniform suspension.

Activating the SAYANA PRESS pre-filled injector

The pre-filled injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid.

Administration

The dose is administered as a SC injection into the anterior thigh or abdomen. When the injection is being given, the pre-filled injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

For full instructions, see Instructions for Use sheet provided with each pack of SAYANA PRESS.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA PRESS should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA PRESS injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA PRESS within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA PRESS, contraceptive coverage will be maintained provided the first SAYANA PRESS injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA PRESS is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties – Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA PRESS is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use**Route of administration**

SAYANA PRESS is not formulated for IM injection. SAYANA PRESS must be given by SC injection.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SC MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical Trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1: Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with IM MPA 150 mg and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1: Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies.

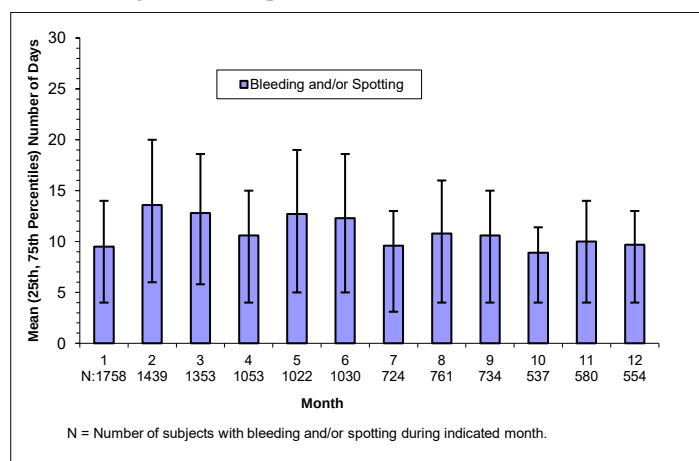
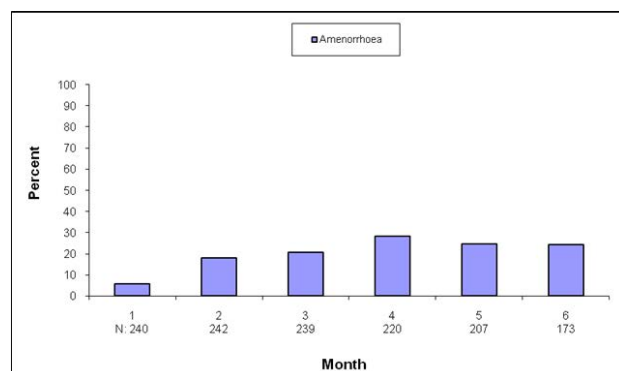


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289).



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of IM MPA injection (150 mg) use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A ~~R~~relative ~~R~~risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented ~~S22~~ : SRR: addition of information regarding meningiomas in alignment with the CDS.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the

maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that SC MPA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SC MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA PRESS is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA PRESS is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA PRESS by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical

trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors.

•Sulfbromophthalein and other liver function test values may be increased slightly.

There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA PRESS.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA PRESS users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – •Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA PRESS is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA PRESS is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM MPA injection (150 mg) may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on IM MPA injection (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with IM MPA injection (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA PRESS has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia

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MedDRA SOC	Event
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

SC MPA: subcutaneous medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.
Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid Syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA PRESS suspension for subcutaneous (SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

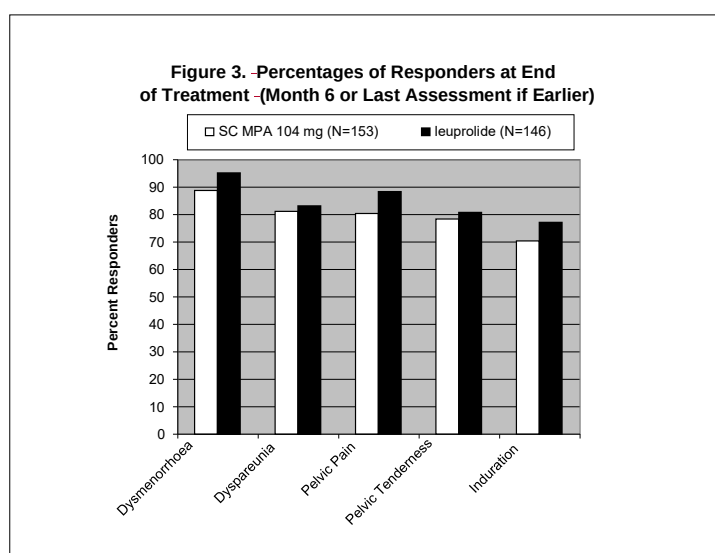
Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent

symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SC MPA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SC MPA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).

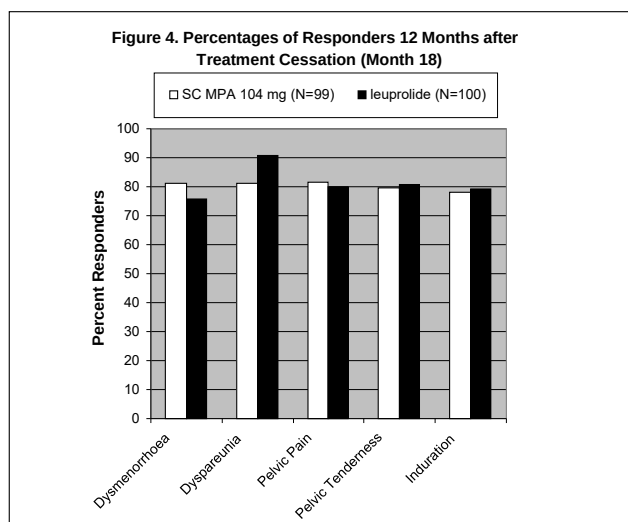


A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No

pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using IM MPA injection (150 mg) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of IM MPA injection (150 mg), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using IM MPA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5: Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception.

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SC MPA women became pregnant while one of the IM MPA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6: Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy.

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of IM MPA injection (150 mg) every 3 months for up to 240 weeks [4.6 years] in adolescent females (12–18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was

discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from IM MPA use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7: Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42):

	C _{max} (ng/mL)	T _{max} (day)	C ₉₁ (min) (ng/mL)	AUC ₀₋₉₁ (ng·day/mL)	AUC _{0-∞} (ng·day/mL)	t _{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration.

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the $C_{\min}$ and the SC dose of MPA appeared to be linear. The mean $C_{\max}$ did not change substantially with increasing dose

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of MPA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women ($n=42$, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA $C_{\max}$ was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough ($C_{\min}$) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ampoule with attached needle (pre-filled injector) contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. -Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA PRESS 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose ampoule with attached needle (pre-filled injector).

The product containing part of the pre-filled injector is made of linear low density polyethylene laminate with a siliconised stainless steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

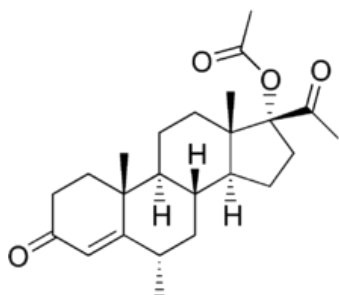
6.6 Special precautions for disposal

A puncture-resistant container should be used. If the product is self-administered, the patient should be told of the importance of proper pre-filled injector and needle disposal and be cautioned against reuse of these items.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: ~~C₂₄H₃₄O₄~~

Molecular weight: ~~386.5~~

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

Commented ~~S22~~ : MEC: update to the website details of the same site

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

~~09 August 2023~~ [DD Month YYYY](#)

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
All	Change in trade name.
4.2, 6.5	Changes to container from pre-filled glass syringe to ampoule with attached needle (pre-filled injector). Addition of Instructions for Use for pre-filled injector.
6.4	Change in storage conditions
6.6	Addition of recommendation of pre-filled injector disposal
4.4	Addition of information regarding meningioma
All	Minor editorial changes

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**AUSTRALIAN PRODUCT INFORMATION –
PROVERA[®] (MEDROXYPROGESTERONE
ACETATE) TABLETS**

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

Commented s22 : MEC: Add acronym of
medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablets contain 2.5 mg, 5 mg, 10 mg, 100 mg, 200 mg, 250 mg or 500 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect:

Lactose monohydrate (2.5, 5 and 10 mg tablets)

Sodium benzoate (100, 200, 250 and 500 mg tablets)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

100 mg tablets: white, scored, marked U467.

200 mg tablets: white, scored, marked U320.

250 mg tablets: white, scored, marked U403.

500 mg tablets: white, capsule-shaped, marked UPJOHN 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with [MPA](#) ~~medroxyprogesterone acetate~~.

Commented [s22](#) : Minor editorial change

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use**Physical examination**

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented s22 SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine

and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use PROVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

PROVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should

consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of PROVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the

control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5, 5, and 10 mg tablets:

calcium stearate
indigo carmine (5 mg tablet)
sunset yellow FCF (2.5 mg tablet)
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose

PROVERA 100, 200, 250, and 500 mg tablets:

docusate sodium
gelatin
isopropyl alcohol
macrogol 400
magnesium stearate
maize starch
microcrystalline cellulose
purified water
sodium benzoate
sodium starch glycollate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PROVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

100 mg tablets: blister packs of 10 and 100 tablets.

200 mg tablets: blister packs of 10 and 60 tablets.

250 mg tablets: blister packs of 10 and 60 tablets.

500 mg tablets: blister packs of 10, 30 and 60 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

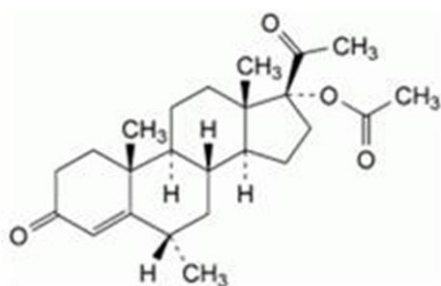
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

10. DATE OF REVISION

~~29 April 2020~~: [DD Month YYYY](#)

® Registered trademark.

Commented [522]: Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CML.

Summary Table of Changes

Section changed	Summary of new information
All	New PI reformat and editorial changes
4.4 and 5.1	Amend BMD recovery time in adolescent females
8	Sponsor address updated
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – RALOVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

Commented s22 : MEC: Add acronym of medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RALOVERA tablets contain 2.5 mg, 5 mg or 10 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect:

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with ~~medroxyprogesterone acetate~~ MPA.

Commented s22 : Minor editorial change

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy (HRT) should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

RALOVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with RALOVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented [REDACTED]: SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of

several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of HRT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of RALOVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use RALOVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of RALOVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of RALOVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

RALOVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than

70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test – the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with RALOVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

RALOVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on RALOVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdose, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of RALOVERA.

However, ~~In~~ a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from

baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and total hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

RALOVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium stearate
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose
sunset yellow FCF (2.5 mg tablet)
indigo carmine (5 mg tablet)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

RALOVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

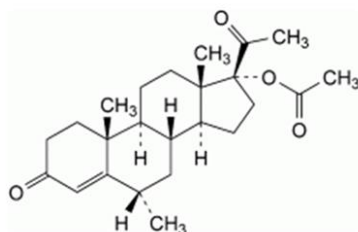
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 October 1993-

Commented s22 : Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CMI.

10. DATE OF REVISION

~~29 April 2020~~.[DD Month YYYY](#)

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
~~All~~	~~New PI reformat and editorial changes~~
~~4.4 and 5.1~~	~~Amend BMD recovery time in adolescent females~~
~~8~~	~~Sponsor address updated~~
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-PROVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use MPA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-PROVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By Month 12, amenorrhoea was reported by 57% of

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).

DEPO-PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-PROVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO PROVERA may significantly decrease the serum concentration of MPA. DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on

MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use – Return of fertility.

Use in pregnancy – Pregnancy Category D

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. In mothers who are breastfeeding and who are treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

- *Cardiac disorders:* Palpitations, myocardial infarction, congestive heart failure.
- *Endocrine disorders:* Prolonged anovulation, Cushingoid syndrome.
- *Eye disorders:* Retinal embolism and thrombosis, diabetic cataract, visual impairment.
- *Gastrointestinal:* Abdominal distension, nausea, constipation, diarrhoea, dry mouth.
- *General disorders and administrative site conditions:* Fatigue, injection site reactions, malaise, hyperpyrexia.
- *Hepatobiliary disorders:* Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
- *Immune system disorders:* Anaphylactic reactions, anaphylactoid reactions, angioedema.
- *Investigations:* Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.
- *Metabolic and nutritional disorders:* Exacerbation of diabetes mellitus, hypercalcaemia.
- *Musculoskeletal and connective tissue disorders:* Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.
- *Nervous System disorders:* Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.
- *Psychiatric disorders:* Depression, insomnia, nervousness.
- *Renal and urinary system disorders:* Glycosuria.
- *Reproductive and breast disorders:* Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

- *Respiratory, thoracic and mediastinal disorders:* Pulmonary embolism.
- *Skin and subcutaneous tissue disorders:* Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.
- *Vascular disorders:* Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

- *Blood and lymphatic system disorders:* Blood dyscrasia, anaemia.

- Cardiac disorders: Tachycardia, chest pain.
- Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.
- General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.
- Hepatobiliary disorders: Jaundice, jaundice cholestatic.
- Immune systems disorders: Drug hypersensitivity reactions.
- Metabolism and nutrition disorders: Changes in appetite.
- Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.
- Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.
- Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.
- Renal and urinary disorders: Genitourinary infections.
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.
- Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.
- Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.
- Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD

was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial.
- 1 x 1 mL pre-filled syringe.

Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

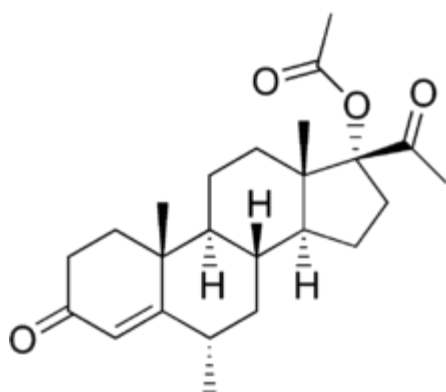
6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in

chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma

	Minor editorial changes
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – DEPO-RALOVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By Month 12, amenorrhoea was reported by 57% of

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-RALOVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-RALOVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when DEPO-RALOVERA is used long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-RALOVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-RALOVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-RALOVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated

with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-RALOVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-RALOVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-RALOVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-RALOVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-RALOVERA. Therefore, if such tests are abnormal in a patient taking DEPO-RALOVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-RALOVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA. DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use - Return of fertility

Use in pregnancy – Pregnancy Category D

DEPO-RALOVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-RALOVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-RALOVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-RALOVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating

- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events reported by fewer than 1% of subjects:

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobiliary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular

maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

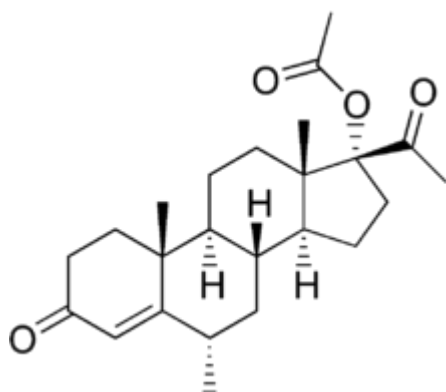
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

31 May 1993

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] PRESS (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS 104 mg/0.65 mL suspension for injection ampoule with attached needle (pre-filled injector) contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA PRESS contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA PRESS is supplied as a single dose ampoule with attached needle (pre-filled injector) containing 104 mg MPA in 0.65 mL suspension for injection. SAYANA PRESS is a white to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA PRESS must be given by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA PRESS is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA PRESS (104 mg) is given. Dosage does not need to be adjusted for body weight.

Method of administration

SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional. If self-administration is planned, the healthcare professional should make an assessment of the patient's skill and competence with the procedure. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate. While on self-injection treatment, it is recommended that the patient visit their doctor at periodic intervals.

Mixing the medicine

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: SAYANA PRESS ampoule with attached needle (pre-filled injector), alcohol swabs and cotton pads.

Each SAYANA PRESS pre-filled injector contains a white to off-white homogeneous suspension. The contents are completely sealed inside the reservoir of the pre-filled injector. As with other parenteral drug products, SAYANA PRESS should be inspected visually for particulate matter and discolouration prior to administration. The pre-filled injector of SAYANA PRESS must be vigorously shaken for at least 30 seconds just before use to create a uniform suspension.

Activating the SAYANA PRESS pre-filled injector

The pre-filled injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid.

Administration

The dose is administered as a SC injection into the anterior thigh or abdomen. When the injection is being given, the pre-filled injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

For full instructions, see Instructions for Use sheet provided with each pack of SAYANA PRESS.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA PRESS should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA PRESS injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA PRESS within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA PRESS, contraceptive coverage will be maintained provided the first SAYANA PRESS injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA PRESS is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties - Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA PRESS is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use**Route of administration**

SAYANA PRESS is not formulated for IM injection. SAYANA PRESS must be given by SC injection.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SC MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1. Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with IM MPA 150 mg and after 2 years post-therapy or 7 years of observation (control)

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1. Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies

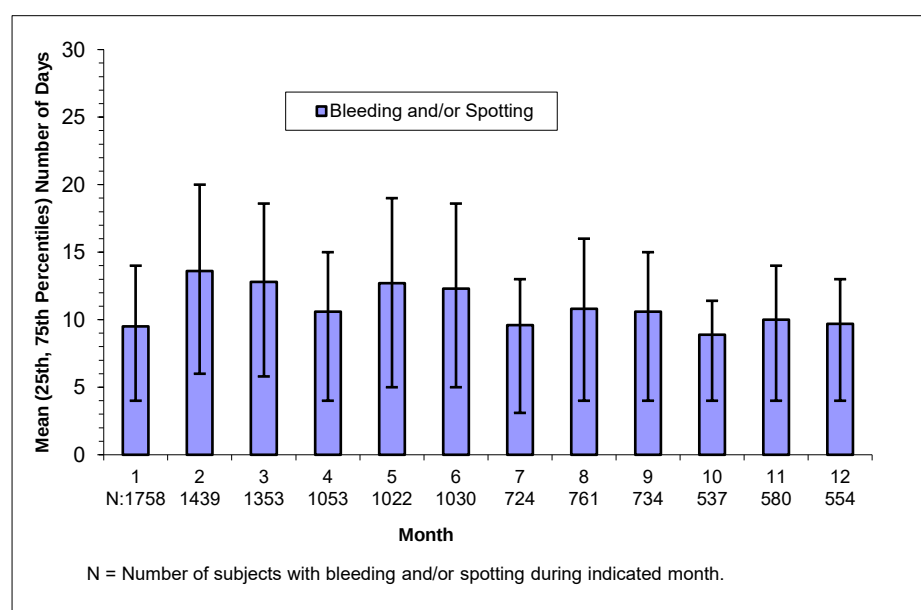
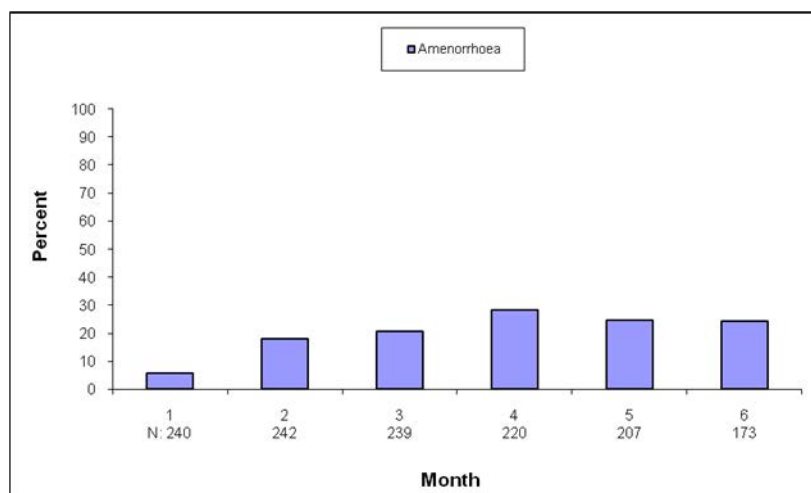


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289)



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of IM MPA injection (150 mg) use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A relative risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the

maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that SC MPA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SC MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA PRESS is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA PRESS is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA PRESS by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical

trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors. Sulfobromophthalein and other liver function test values may be increased slightly. There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA PRESS.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA PRESS users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA PRESS is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA PRESS is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM MPA injection (150 mg) may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on IM MPA injection (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with IM MPA injection (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA PRESS has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia

MedDRA SOC	Event
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

SC MPA: subcutaneous medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA PRESS suspension for subcutaneous (SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

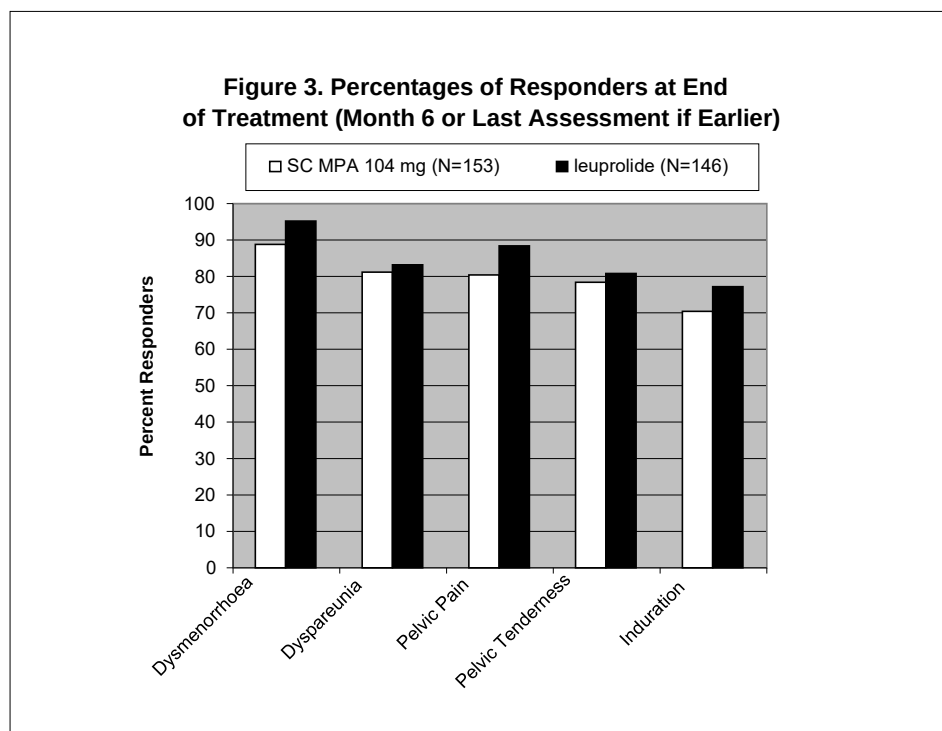
Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SC MPA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide

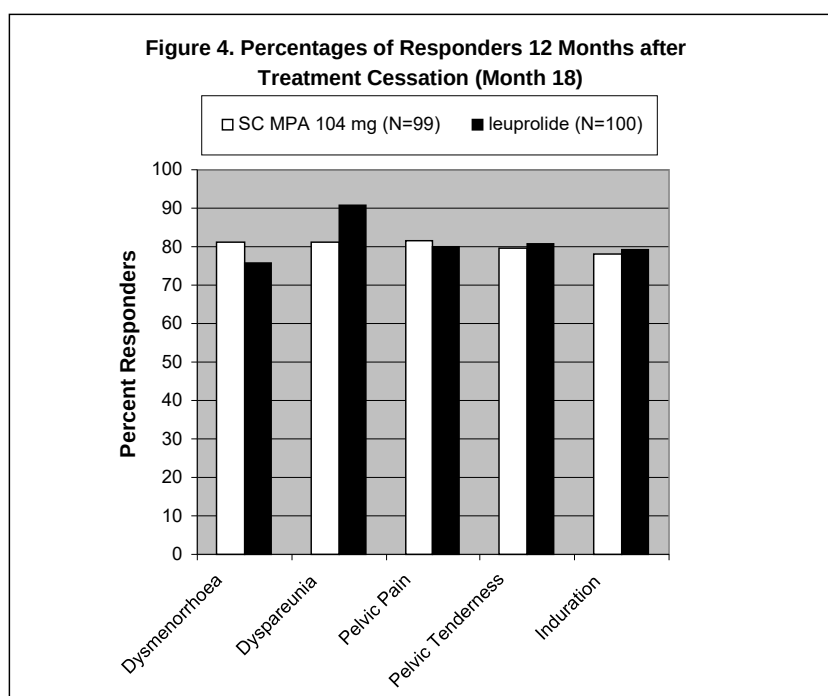
versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SC MPA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using IM MPA injection (150 mg) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of IM MPA injection (150 mg), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using IM MPA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SC MPA women became pregnant while one of the IM MPA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of IM MPA injection (150 mg) every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from IM MPA use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	C₉₁ (min) (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of MPA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ampoule with attached needle (pre-filled injector) contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA PRESS 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose ampoule with attached needle (pre-filled injector).

The product containing part of the pre-filled injector is made of linear low density polyethylene laminate with a siliconised stainless steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

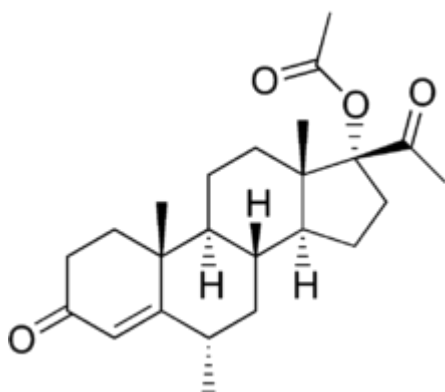
6.6 Special precautions for disposal

A puncture-resistant container should be used. If the product is self-administered, the patient should be told of the importance of proper pre-filled injector and needle disposal and be cautioned against reuse of these items.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: C₂₄H₃₄O₄

Molecular weight: 386.5

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

DD Month YYYY

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
All	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA 104 mg/0.65 mL suspension for injection syringe contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg MPA in 0.65 mL suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA must be given by subcutaneous injection (SC MPA) into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). SAYANA is not formulated for intramuscular (IM) injection.

It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: pre-filled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties - Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use

Route of administration

SAYANA is not formulated for IM injection. SAYANA must be given by SC injection.

Physical examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control

group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1. Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with MPA 150 mg IM and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received MPA injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received MPA Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1. Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies

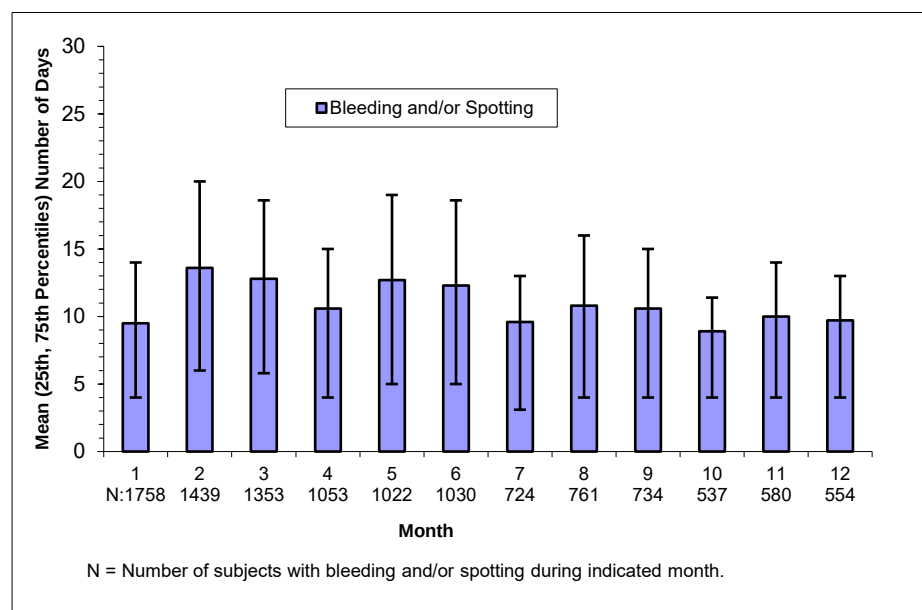
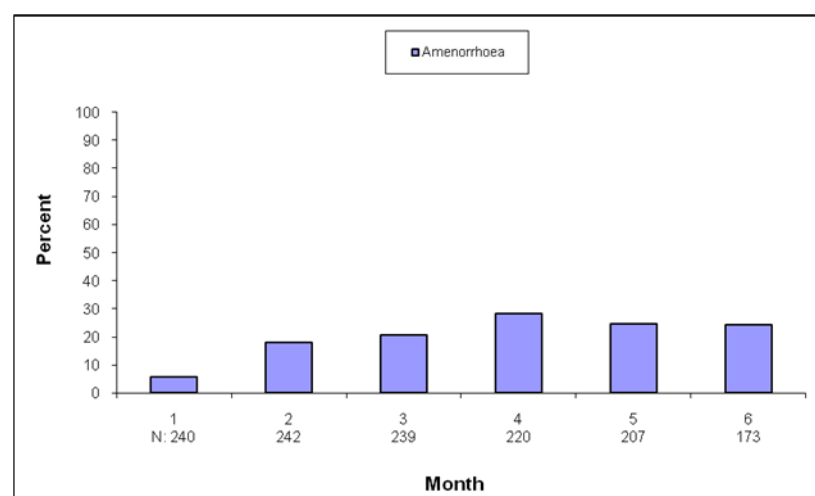


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289)



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of depot MPA IM 150 mg use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the

previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A relative risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors. Sulfobromophthalein and other liver function test values may be increased slightly. There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM injection of 150 mg MPA may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on MPA injection 150 mg IM are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with MPA injection 150 mg IM, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk

have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia

MedDRA SOC	Event
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous(SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was

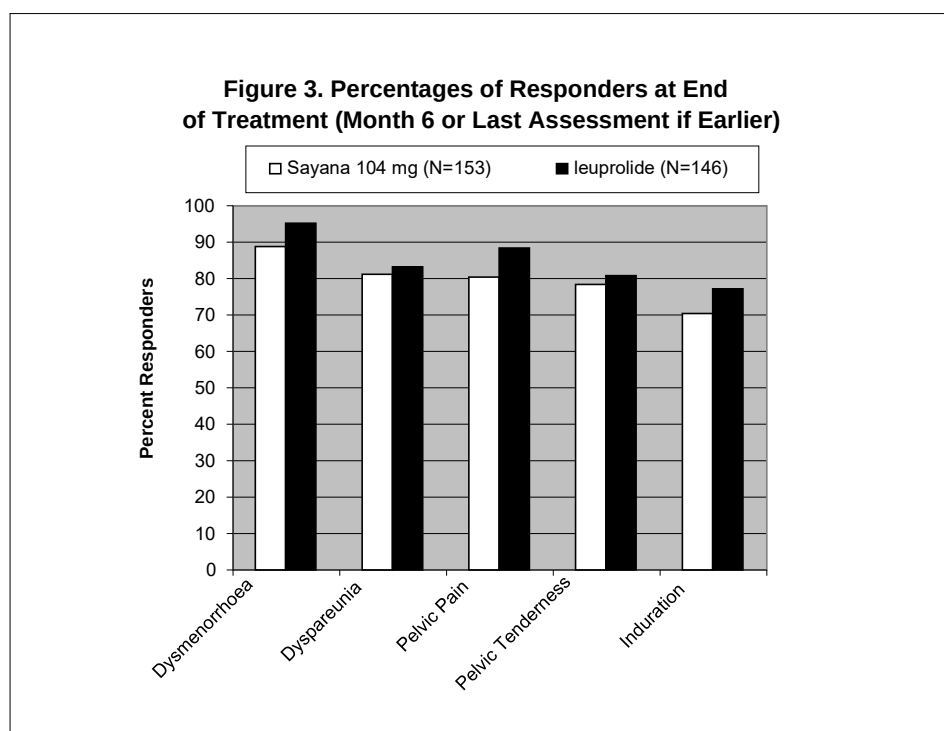
not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

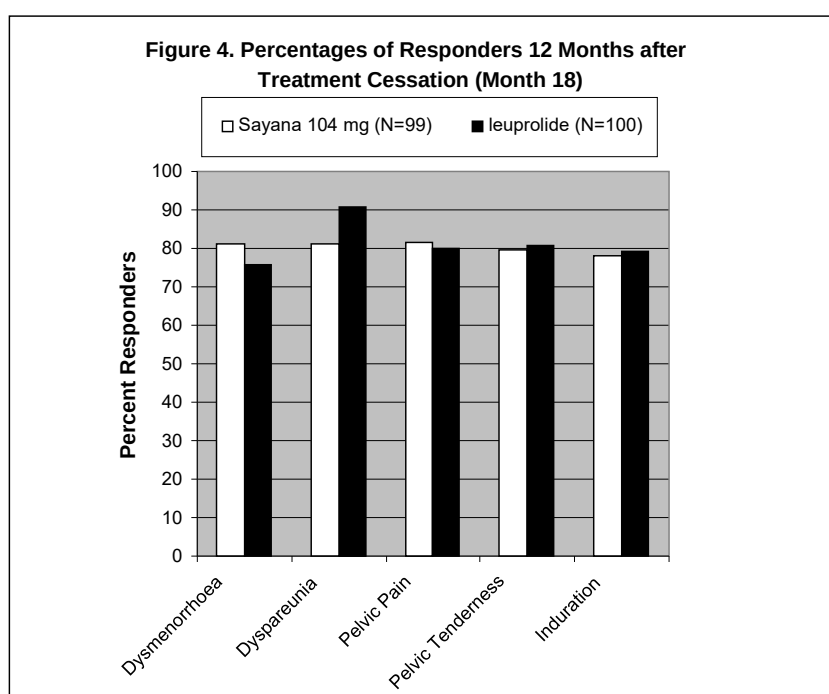
The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SAYANA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SAYANA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using DEPO-PROVERA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SAYANA women became pregnant while one of the DEPO-PROVERA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12–18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from depot medroxyprogesterone acetate (DMPA) use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the $C_{\min}$ and the SC dose of MPA appeared to be linear. The mean $C_{\max}$ did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA $C_{\max}$ was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough ($C_{\min}$) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pre-filled syringe contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

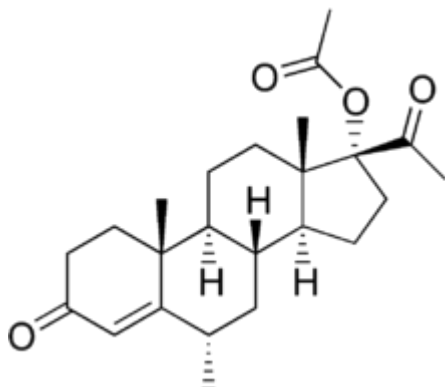
SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate

Molecular formula: C₂₄H₃₄O₄

Molecular weight: 386.5.

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

DD Month YYYY

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
All	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – PROVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablets contain 2.5 mg, 5 mg, 10 mg, 100 mg, 200 mg, 250 mg or 500 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect

Lactose monohydrate (2.5, 5 and 10 mg tablets)

Sodium benzoate (100, 200, 250 and 500 mg tablets)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

100 mg tablets: white, scored, marked U467.

200 mg tablets: white, scored, marked U320.

250 mg tablets: white, scored, marked U403.

500 mg tablets: white, capsule-shaped, marked UPJOHN 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with MPA.

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use**Physical examination**

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine

and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use PROVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

PROVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should

consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of PROVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the

control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5, 5, and 10 mg tablets:

calcium stearate
indigo carmine (5 mg tablet)
sunset yellow FCF (2.5 mg tablet)
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose

PROVERA 100, 200, 250, and 500 mg tablets:

docusate sodium
gelatin
isopropyl alcohol
macrogol 400
magnesium stearate
maize starch
microcrystalline cellulose
purified water
sodium benzoate
sodium starch glycollate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PROVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

100 mg tablets: blister packs of 10 and 100 tablets.

200 mg tablets: blister packs of 10 and 60 tablets.

250 mg tablets: blister packs of 10 and 60 tablets.

500 mg tablets: blister packs of 10, 30 and 60 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

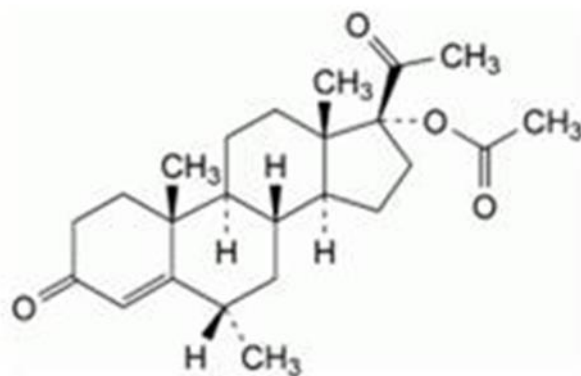
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

10. DATE OF REVISION

DD Month YYYY

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
1, 4.1	Minor editorial changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – RALOVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RALOVERA tablets contain 2.5 mg, 5 mg or 10 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with MPA.

Abnormal uterine bleeding in the absence of organic pathology***Adjunct to estrogen therapy***

Combination hormone replacement therapy (HRT) should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration**Dosage*****Inoperable, recurrent, metastatic, endometrial carcinoma***

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

RALOVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with RALOVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of

several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of HRT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of RALOVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use RALOVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of RALOVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of RALOVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

RALOVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than

70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test – the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with RALOVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

RALOVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on RALOVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of RALOVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from

baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and total hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

RALOVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium stearate
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose
sunset yellow FCF (2.5 mg tablet)
indigo carmine (5 mg tablet)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

RALOVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

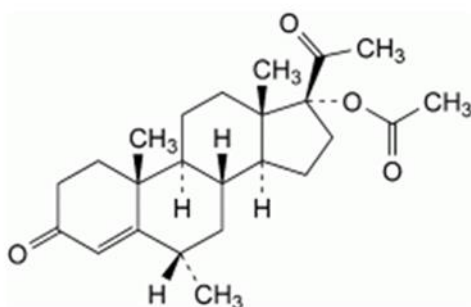
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 October 1993

10. DATE OF REVISION

DD Month YYYY

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

From: s22
To: s22 @pfizer.com
Cc: s22 @pfizer.com
Subject: 9D(2) SRR & 9D(3) MEC - [Approval letter] - PM-2024-00437-1-4 - DEPO-PROVERA/DEPO-RALOVERA/SAYANA/SAYANA PRESS/PROVERA/RALOVERA - medroxyprogesterone acetate injection/tablet - Pfizer Australia Pty Ltd - 26 February 2024 [SEC=OFFICIAL]
Date: Monday, 26 February 2024 3:58:57 PM
Attachments: [\[D24-739958\] 9D\(2\) SRR & 9D\(3\) MEC - \[Approval letter\] - PM-2024-00437-1-4 - DEPO-PROVERA DEPO-RALOVERA SAYANA SAYANA PRESS PROVERA RALOVERA - medroxyprogesterone acetate injection tablet - Pfizer Australia Pty.PDF](#)

Dear s22

Please find attached the approval letter for the above submission.

If you have not yet submitted an eData sequence containing the final PI via email to eSubmissions@health.gov.au, please do so as soon as possible.

Please reply to this email to confirm receipt of letter and advise of any discrepancies today.

Kind regards,

s22

s22

Pharmacist Evaluator
Pharmacist Evaluation Section
Prescription Medicines Authorisation Branch

Email: s22@health.gov.au

Therapeutic Goods Administration
Australian Government Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all of the legislative requirements are met.



Australian Government
Department of Health and Aged Care
 Therapeutic Goods Administration

The Managing Director
 Pfizer Australia Pty Ltd

Clinical File: 2014/040108
 PI File: 2015/003991
 Submission No.: PM-2024-00437-1-4
 Data: [e001209 \(0041-\)](#)

Attention:

s22
s22 @pfizer.com

Dear Sir/Madam,

REQUEST UNDER s. 9D(2) FOR SAFETY-RELATED VARIATION TO THE ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

REQUEST UNDER s. 9D(3) FOR VARIATION TO THE ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

I refer to your request under subsections 9D(2) and 9D(3) of the *Therapeutic Goods Act 1989* (the Act) dated 6 February 2024 to vary the entry of:

- 12300 - DEPO-PROVERA medroxyprogesterone acetate 150 mg/mL aqueous suspension injection vial
- 12331 - PROVERA medroxyprogesterone acetate 100mg tablet blister pack
- 12333 - PROVERA medroxyprogesterone acetate 200mg tablet blister pack
- 12334 - PROVERA medroxyprogesterone acetate 250mg tablet blister pack
- 12336 - PROVERA medroxyprogesterone acetate 500mg tablet blister pack
- 167889 - SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe
- 401610 - DEPO-PROVERA medroxyprogesterone acetate 150 mg/1 mL suspension for injection pre-filled syringe
- 401897 - SAYANA PRESS medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection ampoule with attached needle
- 42932 - PROVERA Medroxyprogesterone acetate 2.5mg tablet blister pack
- 42933 - PROVERA Medroxyprogesterone acetate 5mg tablet blister pack (New Formula)
- 42934 - PROVERA Medroxyprogesterone acetate 10mg tablet blister pack (new embossing)
- 42935 - PROVERA Medroxyprogesterone acetate 10mg tablet bottle (new embossing)
- 44464 - DEPO-RALOVERA medroxyprogesterone acetate 150 mg/1 mL injection vial
- 46527 - RALOVERA medroxyprogesterone acetate 2.5mg tablet blister pack
- 46531 - RALOVERA medroxyprogesterone acetate 5mg tablet blister pack
- 46532 - RALOVERA medroxyprogesterone acetate 10mg tablet blister pack
- 46534 - RALOVERA medroxyprogesterone acetate 10mg tablet bottle

(referred to hereinafter as the product(s)) in the Australian Register of Therapeutic Goods (the ARTG) as described in **Attachment 2a**.

Approval of such a request would result in a decision by the Secretary under subsection 25AA(4) to reflect any variation made under subsection 9D(2) and 9D(3).

Subsections 9D(2), 9D(3), 25AA(4) of the Act can be found online at the following link:
<https://www.legislation.gov.au/Series/C2004A03952>

Decision

As delegate of the Secretary of the Department of Health and Aged Care, I am:

- under subsection 9D(2) and 9D(3) of the Act, varying the information in the entry of the product(s) in the ARTG as requested
- under subsection 25AA(4) of the Act, approving the text of the approved Product Information (PI) for the product(s) to reflect this as set out in the version at **Attachment 2a and 2b** on the basis that the only changes made to the most recently approved PI were those set out in your request of 6 February 2024. This approval is based on the evaluation of the information provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Date of effect

The date of effect of the variation is the date of this approval letter. The “Date of revision” included in the PI is to be the date of this letter.

Action required of you

The approved PI at **Attachment 2b** must be lodged with the TGA **within 2 weeks** of the date of approval of the variation. If the related Consumer Medicine Information (CMI) document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA **within 2 weeks** of the date of the changed PI.

The documents must be lodged in the TGA eBusiness Services system. Information on how to lodge these documents is available at www.ebs.tga.gov.au. The documents must be in text PDF format – scanned PDF documents will **not** be accepted by the system.

Review rights

Details of review rights for the decision under subsection 9D(2), 9D(3) and 25AA(4) are provided at **Attachment 1**.

Your obligations in relation to Product Information etc.

You are reminded that an approved PI for a medicine cannot be changed without the approval of the Secretary under subsection 25AA(4) of the Act.

You are also reminded that the Consumer Medicine Information must comply with the requirements set out in the Therapeutic Goods Regulations 1990, which includes the obligation to ensure the CMI that must be supplied with the medicine is ‘consistent with’ the approved PI.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully,

Electronically signed and authorised by

s22

Delegate of the Secretary

Pharmacist Evaluation Section

Prescription Medicines Authorisation Branch

Email: s22@health.gov.au

26 February 2024

Attachments:

1. Review rights
2. Approved product information for:
 - a. DEPO-PROVERA/DEPO-RALOVERA/SAYANA/SAYANA PRESS
medroxyprogesterone acetate injection (changes highlighted)
PROVERA/RALOVERA medroxyprogesterone acetate tablet (changes highlighted)
 - b. DEPO-PROVERA/DEPO-RALOVERA/SAYANA/SAYANA PRESS
medroxyprogesterone acetate injection (clean)
PROVERA/RALOVERA medroxyprogesterone acetate tablet (clean)

Attachment 1**Request for reconsideration of an initial decision**

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: **'decision.review@health.gov.au'**

Subject: **"<insert name of person/company making request> - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989*"**

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "... - Email 1 of 3", "... - Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of the Act, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-PROVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use MPA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented [522]: SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or

is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-PROVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By ~~at~~Month 12, amenorrhoea was reported by 57% of women, and by ~~at~~Month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).

DEPO-PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or -corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease

- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-PROVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO PROVERA may significantly decrease the serum concentration of MPA. -DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use – Return of fertility.

Use in pregnancy – Pregnancy Category D

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. In mothers who are breastfeeding and who are treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

- *Cardiac disorders*: Palpitations, myocardial infarction, congestive heart failure.
- *Endocrine disorders*: Prolonged anovulation, Cushingoid syndrome.
- *Eye disorders*: Retinal embolism and thrombosis, diabetic cataract, visual impairment.
- *Gastrointestinal*: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.
- *General disorders and administrative site conditions*: Fatigue, injection site reactions, malaise, hyperpyrexia.
- *Hepatobiliary disorders*: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
- *Immune system disorders*: Anaphylactic reactions, anaphylactoid reactions, angioedema.
- *Investigations*: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.
- *Metabolic and nutritional disorders*: Exacerbation of diabetes mellitus, hypercalcaemia.
- *Musculoskeletal and connective tissue disorders*: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

- *Nervous System disorders:* Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.
- *Psychiatric disorders:* Depression, insomnia, nervousness.
- *Renal and urinary system disorders:* Glycosuria.
- *Reproductive and breast disorders:* Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary embolism.
- *Skin and subcutaneous tissue disorders:* Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.
- *Vascular disorders:* Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash

- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

- Blood and lymphatic system disorders: Blood dyscrasia, anaemia.
- Cardiac disorders: Tachycardia, chest pain.
- Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.
- General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.
- Hepatobiliary disorders: Jaundice, jaundice cholestatic.
- Immune systems disorders: Drug hypersensitivity reactions.
- Metabolism and nutrition disorders: Changes in appetite.
- Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.
- Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.
- Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.
- Renal and urinary disorders: Genitourinary infections.
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.
- Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.
- Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.
- Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial.
- 1 x 1 mL pre-filled syringe.

Not all presentations may be marketed.

6.6 Special precautions for disposal

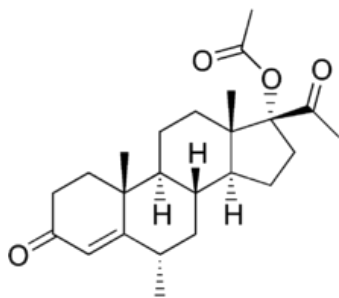
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

Commented [522]: Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CMI.

10. DATE OF REVISION

03 May 2023DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
~~6.4~~	~~Updated special precautions for storage, ‘Do not refrigerate or freeze’.~~
~~6.5~~	~~Updated description for the pre-filled syringe presentation and information on marketed presentations.~~
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – DEPO-RALOVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented [s22]: SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or

is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By ~~at~~Month 12, amenorrhoea was reported by 57% of women, and by ~~at~~Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-RALOVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-RALOVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated ~~when~~ DEPO-RALOVERA is used long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-RALOVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or -corticosteroids

Commented ~~S22~~ : Minor editorial change

- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-RALOVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-RALOVERA in women who were first exposed before the

age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-RALOVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes

should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-RALOVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-RALOVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-RALOVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-RALOVERA. Therefore, if such tests are abnormal in a patient taking DEPO-RALOVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-RALOVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased

- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA. -DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use - Return of fertility

Use in pregnancy – Pregnancy Category D

DEPO-RALOVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-RALOVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-RALOVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period

- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-RALOVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression

- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events reported by fewer than 1% of subjects:

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobiliary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

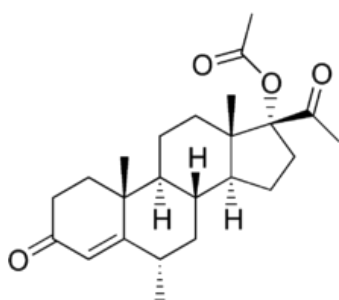
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

Commented [s22] Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CML.

9. DATE OF FIRST APPROVAL

31 May 1993-

10. DATE OF REVISION

~~27 April 2023~~[DD Month YYYY](#)

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
~~Throughout~~	~~Minor editorial changes~~
~~6.4~~	~~Updated special precautions for storage, ‘Do not refrigerate or freeze’.~~
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – SAYANA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA 104 mg/0.65 mL suspension for injection syringe contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

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Excipient(s) with known effect

SAYANA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg MPA in 0.65 mL suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra indicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA must be given by subcutaneous injection (SC MPA) into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). SAYANA is not formulated for intramuscular (IM) injection.

Commented 222 Minor editorial change

It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: pre-filled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from ~~intramuscular (IM) MPA~~ MPA (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for IM MPA (150 mg).

Commented 222 Minor editorial change

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties – Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment

Renal impairment

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use

Route of administration

SAYANA is not formulated for IM injection. SAYANA must be given by SC injection.

Physical examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g. anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical Trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control

group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86% , -4.11% , -4.89% , -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1: Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with MPA 150 mg IM and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received MPA injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received MPA Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during ~~the~~Month 6 and 56.5% experienced amenorrhoea during ~~the~~Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

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Figure 1: Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies.

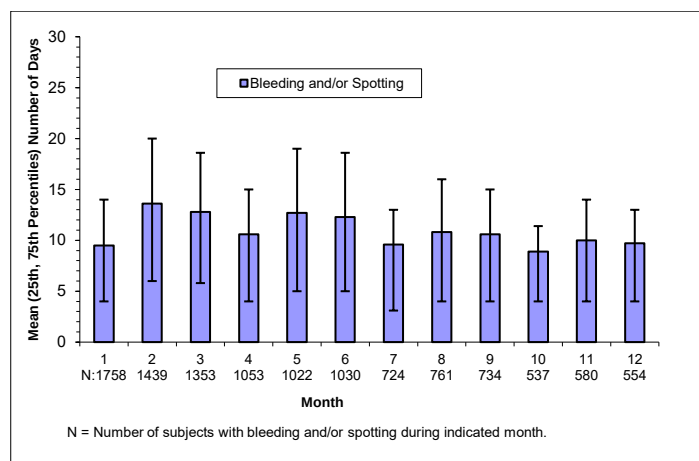
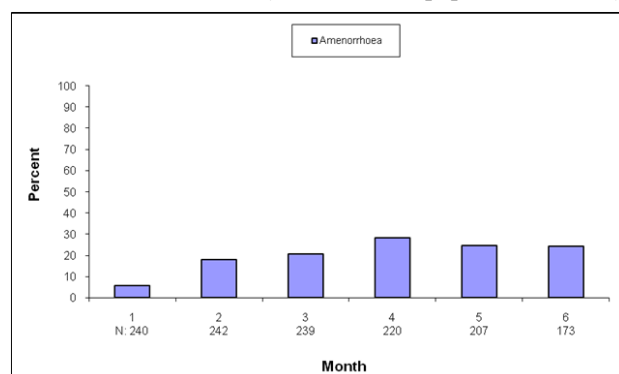


Figure 2: Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289).



Cancer risks

Long-term case-controlled surveillance of depot MPA IM 150 mg use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the

previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A ~~R~~relative ~~R~~risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

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Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors.

• Sulfbromophthalein and other liver function test values may be increased slightly.

There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – [Return of ovulation](#).

Use in pregnancy – Pregnancy Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM injection of 150-mg MPA may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on MPA [Injection 150 mg IM](#) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with MPA injection 150 mg IM, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

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Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

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Table 3. Events associated with the use of SC MPA for endometriosis-associated pain-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations

MedDRA SOC	Event
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

Commented s22 : MEC: Correction of spelling

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous(SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

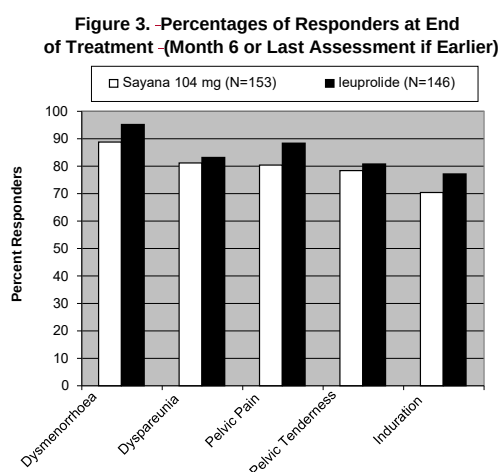
In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomized, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months -or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

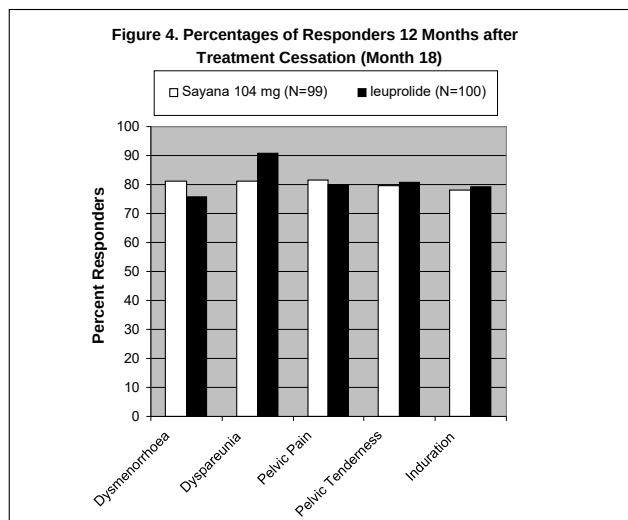
The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SAYANA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SAYANA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using DEPO-PROVERA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception.

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SAYANA women became pregnant while one of the DEPO-PROVERA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6: Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from depot medroxyprogesterone acetate (DMPA) use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42).

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pre-filled syringe contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

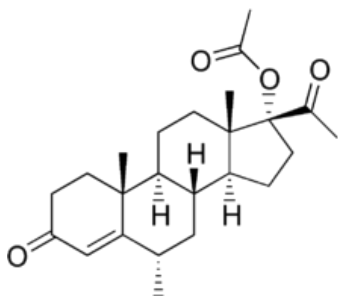
SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: ~~6~~ α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: ~~C~~ $C_{24}H_{34}O_4$.

Molecular weight: ~~3~~386.5.

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

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9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

~~20 April 2023~~ [DD Month YYYY](#)

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Summary Table of Changes

Section changed	Summary of new information
4.8	~~Addition of 'injection site discolouration' as post-marketing ADR~~
6.1	~~Update to the AAN of the excipient, monobasic sodium phosphate monohydrate~~
8	~~Update to sponsor website address~~
4.4	Addition of information regarding meningioma
All	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] PRESS (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS 104 mg/0.65 mL suspension for injection ampoule with attached needle (pre-filled injector) contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA PRESS contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA PRESS is supplied as a single dose ampoule with attached needle (pre-filled injector) containing 104 mg MPA in 0.65 mL suspension for injection. SAYANA PRESS is a white to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18-years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA PRESS must be given by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA PRESS is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA PRESS (104 mg) is given. Dosage does not need to be adjusted for body weight.

Method of administration

SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional. If self-administration is planned, the healthcare professional should make an assessment of the patient's skill and competence with the procedure. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate. While on self-injection treatment, it is recommended that the patient visit their doctor at periodic intervals.

Mixing the medicine

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: SAYANA PRESS ampoule with attached needle (pre-filled injector), alcohol swabs and cotton pads.

Each SAYANA PRESS pre-filled injector contains a white to off-white homogeneous suspension. The contents are completely sealed inside the reservoir of the pre-filled injector. As with other parenteral drug products, SAYANA PRESS should be inspected visually for particulate matter and discolouration prior to administration. The pre-filled injector of SAYANA PRESS must be vigorously shaken for at least 30 seconds just before use to create a uniform suspension.

Activating the SAYANA PRESS pre-filled injector

The pre-filled injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid.

Administration

The dose is administered as a SC injection into the anterior thigh or abdomen. When the injection is being given, the pre-filled injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

For full instructions, see Instructions for Use sheet provided with each pack of SAYANA PRESS.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA PRESS should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA PRESS injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA PRESS within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA PRESS, contraceptive coverage will be maintained provided the first SAYANA PRESS injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA PRESS is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties – Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA PRESS is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use**Route of administration**

SAYANA PRESS is not formulated for IM injection. SAYANA PRESS must be given by SC injection.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SC MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical Trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1: Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with IM MPA 150 mg and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1: Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies.

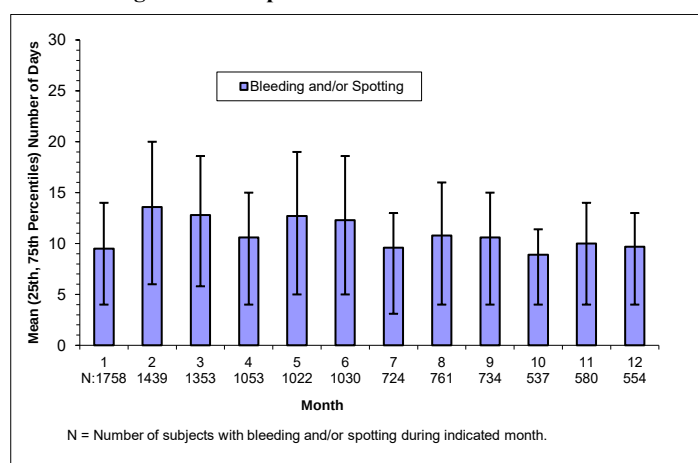
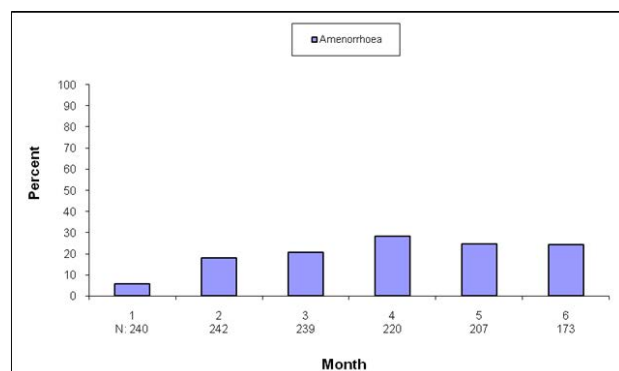


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289).



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of IM MPA injection (150 mg) use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A ~~R~~relative ~~R~~risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented ~~S22~~ : SRR: addition of information regarding meningiomas in alignment with the CDS.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the

maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that SC MPA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SC MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA PRESS is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA PRESS is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA PRESS by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical

trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors.

•Sulfbromophthalein and other liver function test values may be increased slightly.

There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA PRESS.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA PRESS users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – •Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA PRESS is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA PRESS is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM MPA injection (150 mg) may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on IM MPA injection (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with IM MPA injection (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA PRESS has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception.

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia

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MedDRA SOC	Event
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain-

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

SC MPA: subcutaneous medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.
Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA PRESS suspension for subcutaneous (SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

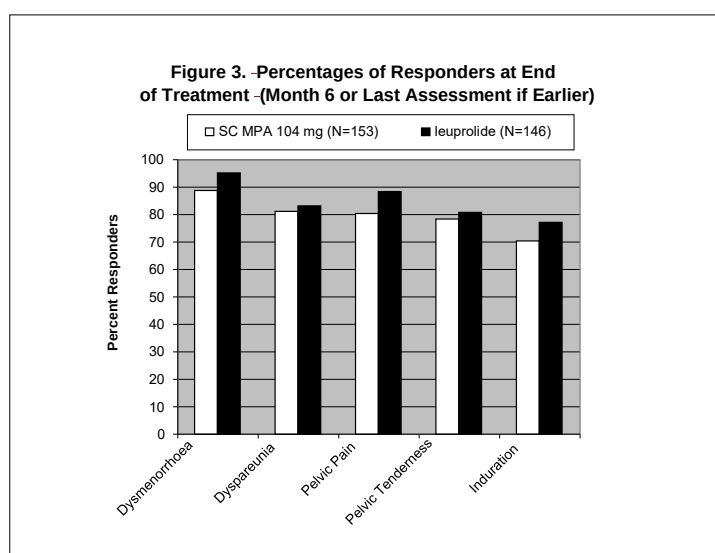
Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent

symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SC MPA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SC MPA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).

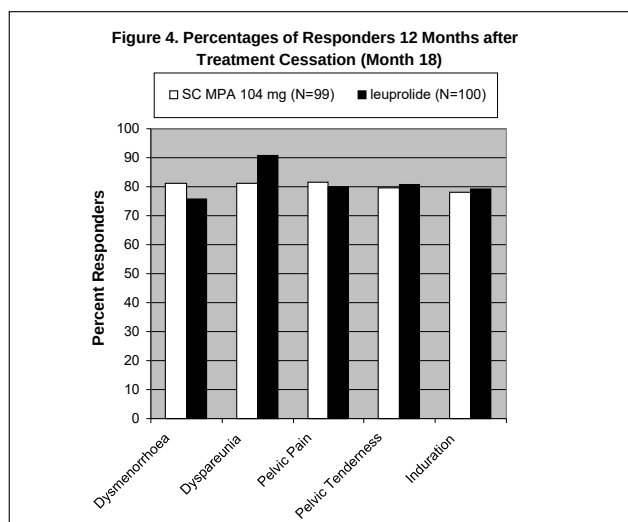


A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No

pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using IM MPA injection (150 mg) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of IM MPA injection (150 mg), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using IM MPA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5: Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception.

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SC MPA women became pregnant while one of the IM MPA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6: Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy.

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of IM MPA injection (150 mg) every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12–18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was

discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from IM MPA use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7: Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42):

	C _{max} (ng/mL)	T _{max} (day)	C _{91 (min)} (ng/mL)	AUC ₀₋₉₁ (ng·day/mL)	AUC _{0-∞} (ng·day/mL)	t _{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration.

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the $C_{\min}$ and the SC dose of MPA appeared to be linear. The mean $C_{\max}$ did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of MPA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women ($n=42$, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA $C_{\max}$ was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough ($C_{\min}$) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ampoule with attached needle (pre-filled injector) contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. -Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA PRESS 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose ampoule with attached needle (pre-filled injector).

The product containing part of the pre-filled injector is made of linear low density polyethylene laminate with a siliconised stainless steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

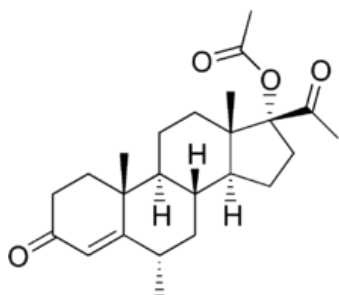
6.6 Special precautions for disposal

A puncture-resistant container should be used. If the product is self-administered, the patient should be told of the importance of proper pre-filled injector and needle disposal and be cautioned against reuse of these items.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: ~~C₂₄H₃₄O₄~~

Molecular weight: ~~386.5~~

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

Commented ~~S22~~ : MEC: update to the website details of the same site

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

~~09 August 2023~~ [DD Month YYYY](#)

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Summary Table of Changes

Section changed	Summary of new information
All	Change in trade name.
4.2, 6.5	Changes to container from pre-filled glass syringe to ampoule with attached needle (pre-filled injector). Addition of Instructions for Use for pre-filled injector.
6.4	Change in storage conditions
6.6	Addition of recommendation of pre-filled injector disposal
4.4	Addition of information regarding meningioma
All	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION – PROVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

Commented [s22]: MEC: Add acronym of medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablets contain 2.5 mg, 5 mg, 10 mg, 100 mg, 200 mg, 250 mg or 500 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect:

Lactose monohydrate (2.5, 5 and 10 mg tablets)

Sodium benzoate (100, 200, 250 and 500 mg tablets)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

100 mg tablets: white, scored, marked U467.

200 mg tablets: white, scored, marked U320.

250 mg tablets: white, scored, marked U403.

500 mg tablets: white, capsule-shaped, marked UPJOHN 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with [MPA](#) ~~medroxyprogesterone acetate~~.

Commented [s22] Minor editorial change

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use**Physical examination**

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented s22 : SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine

and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use PROVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

PROVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should

consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of PROVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the

control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5, 5, and 10 mg tablets:

calcium stearate
indigo carmine (5 mg tablet)
sunset yellow FCF (2.5 mg tablet)
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose

PROVERA 100, 200, 250, and 500 mg tablets:

docusate sodium
gelatin
isopropyl alcohol
macrogol 400
magnesium stearate
maize starch
microcrystalline cellulose
purified water
sodium benzoate
sodium starch glycollate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PROVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

100 mg tablets: blister packs of 10 and 100 tablets.

200 mg tablets: blister packs of 10 and 60 tablets.

250 mg tablets: blister packs of 10 and 60 tablets.

500 mg tablets: blister packs of 10, 30 and 60 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

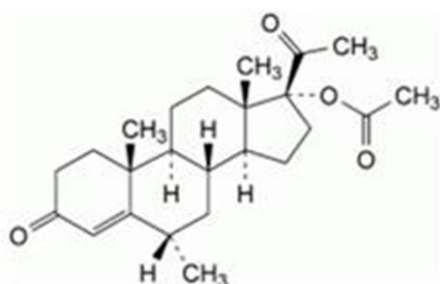
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

10. DATE OF REVISION

~~29 April 2020~~: [DD Month YYYY](#)

® Registered trademark.

Commented [5:22] Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CML.

Summary Table of Changes

Section changed	Summary of new information
All	New PI reformat and editorial changes
4.4 and 5.1	Amend BMD recovery time in adolescent females
8	Sponsor address updated
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

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AUSTRALIAN PRODUCT INFORMATION – RALOVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

Commented [s22]: MEC: Add acronym of medroxyprogesterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RALOVERA tablets contain 2.5 mg, 5 mg or 10 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect:

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with ~~medroxyprogesterone acetate~~ MPA.

Commented [s22]: Minor editorial change

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy (HRT) should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

RALOVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with RALOVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Commented [s22]: SRR: addition of information regarding meningiomas in alignment with the CDS.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of

several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of HRT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of RALOVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use RALOVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of RALOVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of RALOVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

RALOVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than

70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test – the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with RALOVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

RALOVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on RALOVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdose, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of RALOVERA.

However, ~~In~~ a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from

baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and total hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

RALOVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium stearate
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose
sunset yellow FCF (2.5 mg tablet)
indigo carmine (5 mg tablet)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

RALOVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

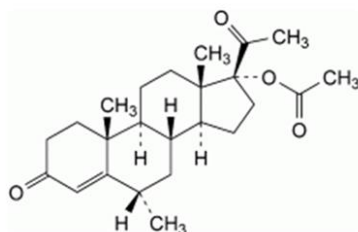
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 October 1993-

Commented [522] Replacement of Pfizer's website address with Pfizer's medical information website address. Pfizer provides assurance that we have full control over the content of the site. The website is to give access to patients and HCPs for medical information queries only. On this site, patients and HCPs are only given access to TGA approved PI and the product CMI.

10. DATE OF REVISION

~~29 April 2020~~.[DD Month YYYY](#)

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
~~All~~	~~New PI reformat and editorial changes~~
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AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-PROVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women, who use MPA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-PROVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-PROVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-PROVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By Month 12, amenorrhoea was reported by 57% of

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-PROVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-PROVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-PROVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years at the total hip and 4.6 years at the femoral neck after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).

DEPO-PROVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-PROVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-PROVERA use.

The overall RR of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-PROVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-PROVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-PROVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-PROVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-PROVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-PROVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-PROVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-PROVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-PROVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-PROVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-PROVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-PROVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO PROVERA may significantly decrease the serum concentration of MPA. DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on

MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use – Return of fertility.

Use in pregnancy – Pregnancy Category D

DEPO-PROVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-PROVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-PROVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-PROVERA. In mothers who are breastfeeding and who are treated with DEPO-PROVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

- *Cardiac disorders:* Palpitations, myocardial infarction, congestive heart failure.
- *Endocrine disorders:* Prolonged anovulation, Cushingoid syndrome.
- *Eye disorders:* Retinal embolism and thrombosis, diabetic cataract, visual impairment.
- *Gastrointestinal:* Abdominal distension, nausea, constipation, diarrhoea, dry mouth.
- *General disorders and administrative site conditions:* Fatigue, injection site reactions, malaise, hyperpyrexia.
- *Hepatobiliary disorders:* Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).
- *Immune system disorders:* Anaphylactic reactions, anaphylactoid reactions, angioedema.
- *Investigations:* Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.
- *Metabolic and nutritional disorders:* Exacerbation of diabetes mellitus, hypercalcaemia.
- *Musculoskeletal and connective tissue disorders:* Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.
- *Nervous System disorders:* Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.
- *Psychiatric disorders:* Depression, insomnia, nervousness.
- *Renal and urinary system disorders:* Glycosuria.
- *Reproductive and breast disorders:* Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

- *Respiratory, thoracic and mediastinal disorders:* Pulmonary embolism.
- *Skin and subcutaneous tissue disorders:* Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.
- *Vascular disorders:* Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-PROVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-PROVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events were reported by fewer than 1% of subjects

- *Blood and lymphatic system disorders:* Blood dyscrasia, anaemia.

- Cardiac disorders: Tachycardia, chest pain.
- Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.
- General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.
- Hepatobiliary disorders: Jaundice, jaundice cholestatic.
- Immune systems disorders: Drug hypersensitivity reactions.
- Metabolism and nutrition disorders: Changes in appetite.
- Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.
- Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.
- Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.
- Renal and urinary disorders: Genitourinary infections.
- Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.
- Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.
- Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.
- Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-PROVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-PROVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-PROVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-PROVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-PROVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-PROVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD

was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-PROVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-PROVERA 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial.
- 1 x 1 mL pre-filled syringe.

Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

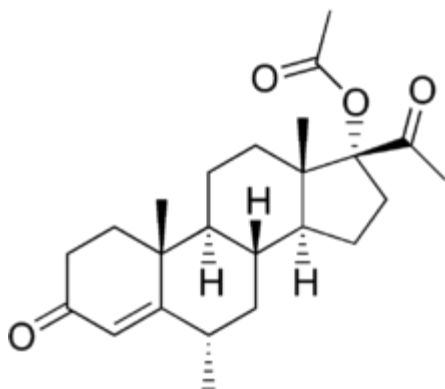
6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in

chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma

	Minor editorial changes
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – DEPO-RALOVERA® (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg medroxyprogesterone acetate (MPA).

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600 mg to 1200 mg weekly followed by 450 mg to 600 mg every 1 to 4 weeks for maintenance.

Breast carcinoma

IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

Endometriosis

50 mg weekly or 100 mg every 2 weeks by IM injection for at least 6 months.

Contraception (ovulation suppression)

150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the time of the first administration it is recommended that this injection is given only:

- during the first 5 days after the onset of normal menstrual period
- within 5 days post-partum if not breast-feeding or
- if breast-feeding, at 6 weeks post-partum, after having excluded pregnancy.

If the period between injections is greater than 14 weeks, the physician should determine that the patient is not pregnant before administering the drug.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.

Gluteal infiltration and abscess formation may occur with IM administration. This complication appears to be particularly related to the volume administered and careful attention to injection technique should be observed. If large volumes are to be given, i.e., greater than 2.5 mL, then divided administration into several sites is recommended. It is also important that the suspension be shaken well before use and administered by deep IM injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental estrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral estrogens in the equivalent of 0.05 mg to 0.1 mg ethinylestradiol daily for 7 to 21 days. This therapy can be continued for 1 to 2 cycles, but should not be considered for long-term administration.

If abnormal bleeding persists, appropriate investigation should be instituted to rule out the possibility of organic pathology.

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs as well as Papanicolaou smear.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By Month 12, amenorrhoea was reported by 57% of

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

Infertility and anovulation with amenorrhoea and/or erratic menstrual patterns may persist for periods of up to 18 months and occasionally longer following either single or multiple injections of DEPO-RALOVERA.

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum estrogen levels and is associated with a statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

In adult females, BMD was observed for a period of 2 years after DEPO-RALOVERA injection was discontinued and mean BMD increased but deficits at the total hip, femoral neck and lumbar spine remain.

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases. Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when DEPO-RALOVERA is used long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity. Since loss of BMD may occur in premenopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Other contraceptive methods or endometriotic treatments should be considered in the risk/benefit analysis for the use of DEPO-RALOVERA in women with osteoporotic risk factors such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

There are no studies on the BMD effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long-term.

It is recommended that all patients have adequate calcium and Vitamin D intake.

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89) has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA. The risk of breast cancer was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

The overall, non-significant, relative rate of invasive squamous cell cervical cancer in women who ever used DEPO-RALOVERA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in RR estimates of invasive squamous cell cervical cancer has been associated with the use of DEPO-RALOVERA in women who were first exposed before the age of 35 years (RR of 1.22 to 1.28, 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated

with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Ectopic pregnancy

As with all forms of hormonal contraception, healthcare providers should be alert to the possibility of an ectopic pregnancy among women using DEPO-RALOVERA who become pregnant or complain of severe abdominal pain.

Sexually transmitted infections

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

In all situations where cessation of therapy is warranted, the physician should be aware of the slow elimination of the depot formulation.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA possesses adrenocorticoid activity.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with IM MPA.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Weight changes

There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kg women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kg. Women who completed 2 years of therapy gained an average of 3.68 kg. Women who completed 4 years gained an average of 6.3 kg. Women who completed 6 years gained an average of 7.5 kg. Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of fertility

DEPO-RALOVERA has a prolonged contraceptive effect. In a large US study of women who discontinued use of DEPO-RALOVERA to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 65% of women who do become pregnant may conceive within 12 months. 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued DEPO-RALOVERA and were lost to follow-up or changed their mind.

Liver function

Certain endocrine and possible liver function tests may be affected by treatment with DEPO-RALOVERA. Therefore, if such tests are abnormal in a patient taking DEPO-RALOVERA, it is recommended that they be repeated after the drug has been withdrawn. If jaundice develops, consideration should be given to not readminister DEPO-RALOVERA.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see Section 4.2 Dose and method of administration).

General

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

MPA used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see Section 4.3 Contraindications).

Use in renal impairment

See Section 4.4 Special warnings and precautions for use - Fluid retention.

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for post-menarcheal adolescent and adult females.

Effects on laboratory tests

The following laboratory tests may be affected by the use of DEPO-RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered
- sex hormone-binding-globulin concentrations are decreased
- coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA. DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised in vitro primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use - Return of fertility

Use in pregnancy – Pregnancy Category D

DEPO-RALOVERA IS NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

Studies in animals have shown that progestogens, including MPA, may have an adverse effect on the developing fetus, including teratogenicity and fetotoxicity.

In addition, other animal studies have shown that high doses of progestogens can cause masculinisation of the female fetus.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risks to female fetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to MPA *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

If DEPO-RALOVERA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

To ensure that DEPO-RALOVERA is not administered inadvertently to a pregnant woman, it is important that the first injection only be given:

- during the first 5 days after the onset of a normal menstrual period
- within 5 days post-partum if not breast feeding and
- if breast feeding, at the sixth week post-partum, after having excluded pregnancy.

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See Section 4.2 Dose and method of administration. See also Section 4.4 Special warnings and precautions for use.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The following events are associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: Palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

Eye disorders: Retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal: Abdominal distension, nausea, constipation, diarrhoea, dry mouth.

General disorders and administrative site conditions: Fatigue, injection site reactions, malaise, hyperpyrexia.

Hepatobiliary disorders: Liver disorders, hepatic function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorders: Anaphylactic reactions, anaphylactoid reactions, angioedema.

Investigations: Bone density decreased, blood pressure increased, weight increased, weight decreased, elevations of serum calcium and potassium levels, increases in white cell and platelet counts, decreased glucose tolerance.

Metabolic and nutritional disorders: Exacerbation of diabetes mellitus, hypercalcaemia.

Musculoskeletal and connective tissue disorders: Arthralgia, gluteal infiltration and abscess formation (this reaction appears to be related to the volume of agent administered and the highest frequency of this complication occurs with large volumes, i.e., greater than 2.5 mL), back pain, muscle spasm.

Nervous System disorders: Cerebral infarction, somnolence, dizziness, headache, adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), tremor.

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

Reproductive and breast disorders: Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), breast pain, breast tenderness, galactorrhoea, vaginal discharge, changes in the position of the transformation zone, cervical discharge.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

Skin and subcutaneous tissue disorders: Urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight fluctuation
- nervousness
- headache
- asthenia (weakness or fatigue).

Adverse reactions reported by 1% to 5% of subjects using DEPO-RALOVERA were:

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating

- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

The following events reported by fewer than 1% of subjects:

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

General disorders and administrative site conditions: Pyrexia, chills, excessive thirst, pain at injection site.

Hepatobiliary disorders: Jaundice, jaundice cholestatic.

Immune systems disorders: Drug hypersensitivity reactions.

Metabolism and nutrition disorders: Changes in appetite.

Musculoskeletal and connective tissue disorders: Scleroderma, osteoporosis.

Nervous system disorders: Seizures, facial palsy, paralysis, somnolence, syncope.

Psychiatric disorders: Confusion, euphoria, loss of concentration, changes in libido.

Renal and urinary disorders: Genitourinary infections.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, dyspnoea, asthma, dysphonia.

Reproductive and breast disorder: Galactorrhoea, dyspareunia, dyspareunia, vaginal cysts, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, accidental pregnancy, uterine cervical erosions, cervical cancer, dysmenorrhoea, uterine hyperplasia.

Skin and subcutaneous tissue disorders: Chloasma, hirsutism, dry skin, hyperhidrosis, abnormal body odour.

Vascular disorders: Thrombophlebitis, deep vein thrombosis, varicose veins.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction and injection site pain/tenderness were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular

maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

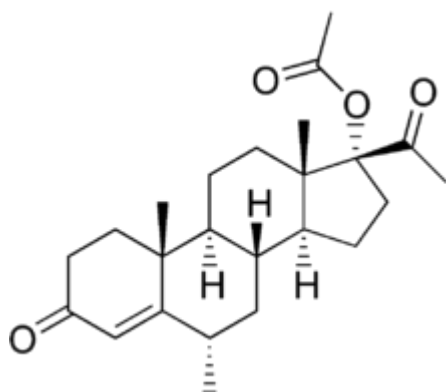
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, the molecular formula is C₂₄H₃₄O₄ and its molecular weight is 386.52. The structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

31 May 1993

10. DATE OF REVISION

DD Month YYYY

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Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] PRESS (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA PRESS 104 mg/0.65 mL suspension for injection ampoule with attached needle (pre-filled injector) contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA PRESS contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA PRESS is supplied as a single dose ampoule with attached needle (pre-filled injector) containing 104 mg MPA in 0.65 mL suspension for injection. SAYANA PRESS is a white to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA PRESS must be given by subcutaneous (SC) injection into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA PRESS is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA PRESS (104 mg) is given. Dosage does not need to be adjusted for body weight.

Method of administration

SAYANA PRESS may be administered by a healthcare professional (HCP) or when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary in accordance with local clinical guidance.

Administration of SAYANA PRESS should be initiated under the supervision of a healthcare professional. If self-administration is planned, the healthcare professional should make an assessment of the patient's skill and competence with the procedure. After proper training in injection technique and schedule of administration, patients may self-inject with SAYANA PRESS if their HCP determines that it is appropriate. While on self-injection treatment, it is recommended that the patient visit their doctor at periodic intervals.

Mixing the medicine

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: SAYANA PRESS ampoule with attached needle (pre-filled injector), alcohol swabs and cotton pads.

Each SAYANA PRESS pre-filled injector contains a white to off-white homogeneous suspension. The contents are completely sealed inside the reservoir of the pre-filled injector. As with other parenteral drug products, SAYANA PRESS should be inspected visually for particulate matter and discolouration prior to administration. The pre-filled injector of SAYANA PRESS must be vigorously shaken for at least 30 seconds just before use to create a uniform suspension.

Activating the SAYANA PRESS pre-filled injector

The pre-filled injector must be activated before use. The activation process pierces an internal seal so that the medicine can come out through the needle when the reservoir is squeezed. The liquid does not completely fill the reservoir. There is a small bubble of air above the liquid.

Administration

The dose is administered as a SC injection into the anterior thigh or abdomen. When the injection is being given, the pre-filled injector must be used with the needle downwards. This ensures that the full dose of liquid is delivered out through the needle. **The medication should be injected slowly for 5-7 seconds.**

For full instructions, see Instructions for Use sheet provided with each pack of SAYANA PRESS.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA PRESS should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA PRESS injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA PRESS within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA PRESS, contraceptive coverage will be maintained provided the first SAYANA PRESS injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA PRESS is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties - Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA PRESS is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA PRESS is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use**Route of administration**

SAYANA PRESS is not formulated for IM injection. SAYANA PRESS must be given by SC injection.

Physical examination

The pre-treatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of SC MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1. Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with IM MPA 150 mg and after 2 years post-therapy or 7 years of observation (control)

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received IM MPA injection (150 mg) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1. Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies

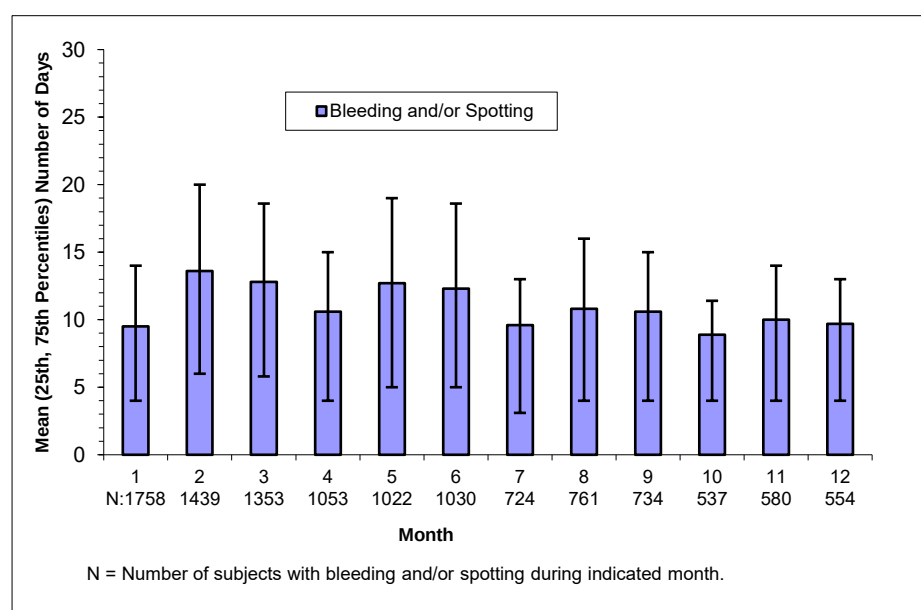
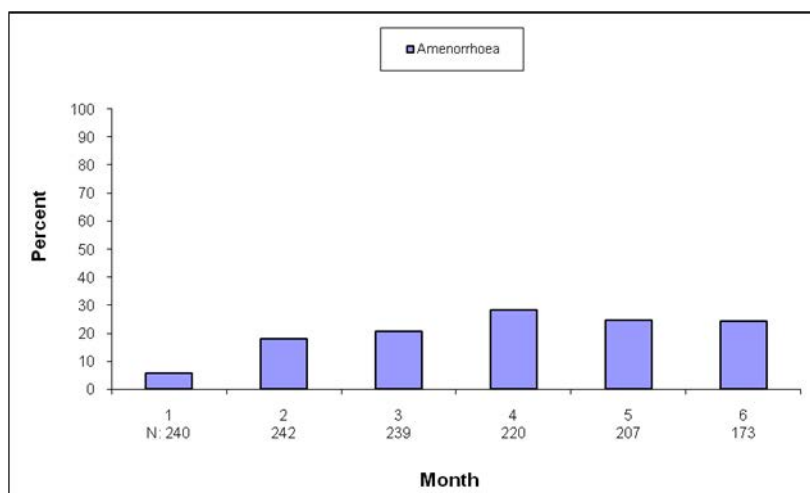


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289)



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of IM MPA injection (150 mg) use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A relative risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the

maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that SC MPA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, SC MPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA PRESS is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA PRESS is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA PRESS by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical

trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors. Sulfobromophthalein and other liver function test values may be increased slightly. There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA PRESS.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA PRESS users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA PRESS is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA PRESS is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM MPA injection (150 mg) may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on IM MPA injection (150 mg) are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with IM MPA injection (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA PRESS has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia

MedDRA SOC	Event
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0

Adverse Event ++	SC MPA (N=153)		Leuprolide (N=146)	
	n	%	n	%
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

SC MPA: subcutaneous medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA PRESS suspension for subcutaneous (SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

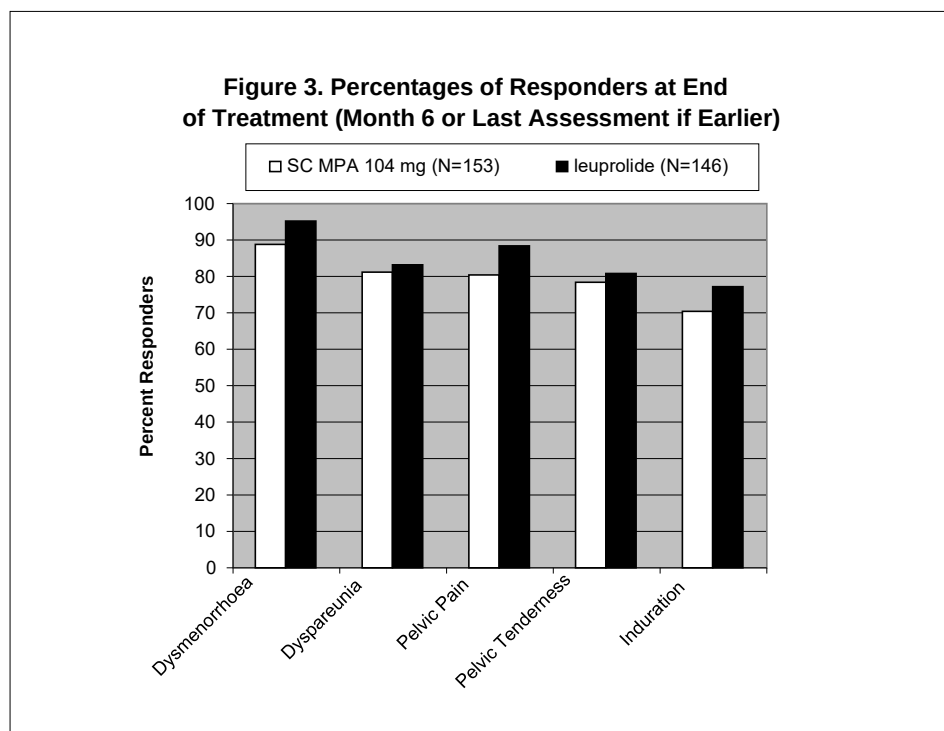
Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SC MPA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide

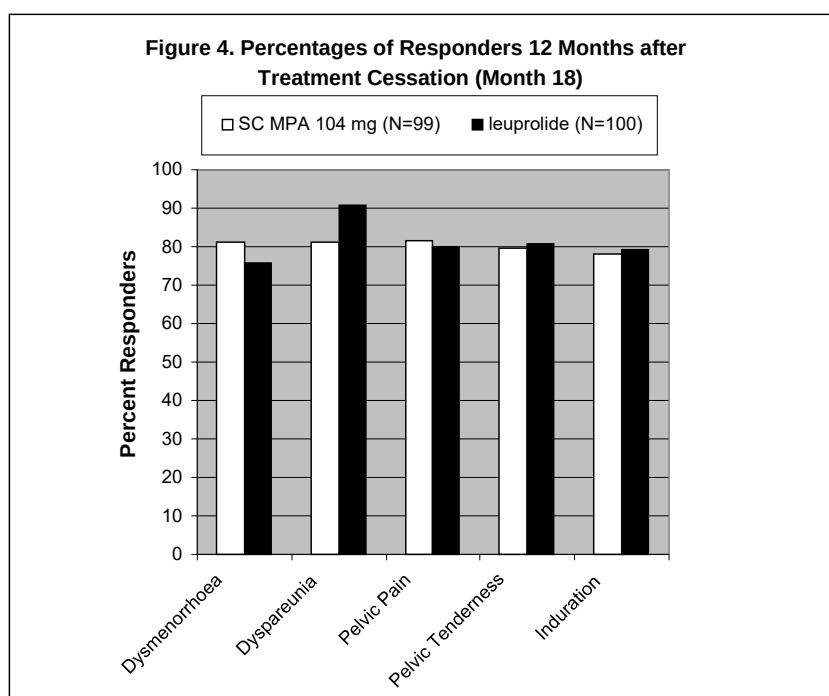
versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SC MPA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using IM MPA injection (150 mg) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of IM MPA injection (150 mg), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using IM MPA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SC MPA women became pregnant while one of the IM MPA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of IM MPA injection (150 mg) every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12-18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from IM MPA use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of MPA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA C_{max} was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ampoule with attached needle (pre-filled injector) contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

SAYANA PRESS 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose ampoule with attached needle (pre-filled injector).

The product containing part of the pre-filled injector is made of linear low density polyethylene laminate with a siliconised stainless steel 23 gauge thin wall needle attached via a low density polyethylene port and valve.

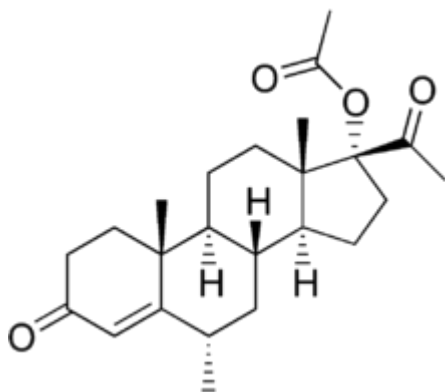
6.6 Special precautions for disposal

A puncture-resistant container should be used. If the product is self-administered, the patient should be told of the importance of proper pre-filled injector and needle disposal and be cautioned against reuse of these items.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate.

Molecular formula: C₂₄H₃₄O₄

Molecular weight: 386.5

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

DD Month YYYY

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
All	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – SAYANA[®] (MEDROXYPROGESTERONE ACETATE)

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAYANA 104 mg/0.65 mL suspension for injection syringe contains 104 mg of MPA.

MPA is a white to off-white, odourless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Excipient(s) with known effect

SAYANA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SAYANA is supplied as a single dose pre-filled syringe containing 104 mg MPA in 0.65 mL suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis, where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Contraception (ovulation suppression)

For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use MPA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Contraception and endometriosis

Route of administration

SAYANA must be given by subcutaneous injection (SC MPA) into the anterior thigh or abdomen, once every 3 months (12 to 14 weeks). **SAYANA is not formulated for intramuscular (IM) injection.**

It is very important that the entire dose of SAYANA (104 mg) is given. Dosage does not need to be adjusted for body weight.

Ensure that the medication is at room temperature because the suspension may become hard and viscous at low temperatures. Ensure that the following components are available: pre-filled syringe, needle with plastic cap, alcohol swabs and cotton pads. Each SAYANA pre-filled syringe contains a white to off-white homogeneous suspension. As with other parenteral drug products, SAYANA should be inspected visually for particulate matter and discoloration prior to administration. The pre-filled syringe of SAYANA must be vigorously shaken for at least 1 minute just before use to create a uniform suspension. To avoid needle detachment and/or the plunger sticking to the barrel, the suspension should be injected slowly.

This product is for single use in one patient only. Discard any residue.

First injection

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are not breast-feeding should be given the first injection within 5 days postpartum. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

If the injection is carried out according to these instructions, contraceptive cover may be expected from the day the injection is administered and no additional contraceptive measure is required.

Second and subsequent injections

Dosing is every 12 to 14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

If using for contraception and switching from another method

When switching from other contraceptive methods, SAYANA should be given in a manner that ensures continuous contraceptive coverage until the first SAYANA injection is administered. For example, patients switching from combined (estrogen plus progestogen) contraceptives should have their first injection of SAYANA within 7 days after the last day of using that method (7 days after taking the last active pill, or removing the patch or ring). If switching from IM MPA (150 mg) to SAYANA, contraceptive coverage will be maintained provided the first SAYANA injection is given within the prescribed dosing period for IM MPA (150 mg).

BMD should be evaluated when considering contraceptive treatment beyond 2 years.

If using for the treatment of endometriosis

Treatment for longer than two years is not recommended, due to the impact of long-term MPA on BMD. If symptoms return after discontinuation of treatment, BMD should be evaluated prior to retreatment.

Children and adolescents

SAYANA is not indicated before menarche. Data in adolescent females (12-18 years) is available for IM administration of MPA (see Section 5.1 Pharmacological properties - Clinical trials and 4.4 Special warnings and precautions for use). Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.

Dosage adjustment***Renal impairment***

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA. However, since MPA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment is considered necessary in women with renal dysfunction.

Hepatic impairment

No formal studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, MPA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe hepatic insufficiency.

4.3 Contraindications

SAYANA is contraindicated in patients with:

- known sensitivity to MPA or any of the excipients in the injection (see Section 6.1 List of excipients)
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- known or suspected malignancy of the breast or genital organs
- undiagnosed vaginal bleeding
- severe hepatic impairment
- metabolic bone disease
- patients with active thromboembolic disease (thrombophlebitis, thromboembolic disorders, cerebral apoplexy) or with current or past history of cerebrovascular disease
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- severe uncontrolled hypertension.

4.4 Special warnings and precautions for use

Route of administration

SAYANA is not formulated for IM injection. SAYANA must be given by SC injection.

Physical examination

The pretreatment physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Loss of BMD

Use of SC MPA reduces serum estrogen levels and is associated with significant loss of BMD due to the known effect of estrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use and appears to be at least partially reversible after SC MPA is discontinued and ovarian estrogen production increases.

This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SC MPA by adolescent women will reduce peak bone mass and increase the risk for osteoporotic fracture late in life.

In adolescents, use of SC MPA is only indicated when other methods of contraception have been discussed with the patient and are considered to be unsuitable or unacceptable due to the unknown long-term effects of bone loss associated with SC MPA during the critical period of bone accretion.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

Other contraceptive methods or endometrial treatments should be considered in the risk/benefit analysis for the use of MPA injection in women with significant lifestyle and/or medical risk factors for osteoporosis such as:

- chronic alcohol and/or tobacco use
- chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- metabolic bone disease
- strong family history of osteoporosis.

The decrease in BMD that occurs during pregnancy and/or lactation should also be taken into consideration prior to use of SC MPA. For further information on BMD changes in both adult and adolescent females, as reported in recent clinical studies, refer to Section 5.1 Pharmacodynamic properties – Clinical trials. Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

In a controlled, clinical study adult women using IM MPA for up to 5 years showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control

group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar. Please refer to Table 1 for further details.

Table 1. Mean percent change from baseline in BMD in adults by skeletal site and cohort after 5 Years of therapy with MPA 150 mg IM and after 2 years post-therapy or 7 years of observation (control).

Time in study	Spine		Total hip		Femoral neck	
	MPA	Control	MPA	Control	MPA	Control
5 years*	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 years**	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

*The treatment group consisted of women who received MPA injection (150 mg IM) for 5 years and the control group consisted of women who did not use hormonal contraception for this time period.

** The treatment group consisted of women who received MPA Injection (150 mg IM) for 5 years and were then followed up for 2 years post-use and the control group consisted of women who did not use hormonal contraceptive for 7 years.

Bleeding irregularities

Most women using SC MPA experienced changes in menstrual bleeding patterns such as amenorrhoea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. Patients should be appropriately counselled concerning the likelihood of menstrual disturbance and the potential delay in return to ovulation. If abnormal bleeding associated with SC MPA persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued using SC MPA, fewer experienced irregular bleeding and more experienced amenorrhoea. In the three contraception studies, 39.0% of women experienced amenorrhoea during Month 6 and 56.5% experienced amenorrhoea during Month twelve.

The changes in menstrual patterns in the contraception and endometriosis trials are presented in Figures 1 and 2.

Figure 1. Mean (25th, 75th percentiles) number of bleeding and/or spotting days in the subgroup of women with bleeding and/or spotting by month for women treated with SC MPA 104 mg in contraception studies

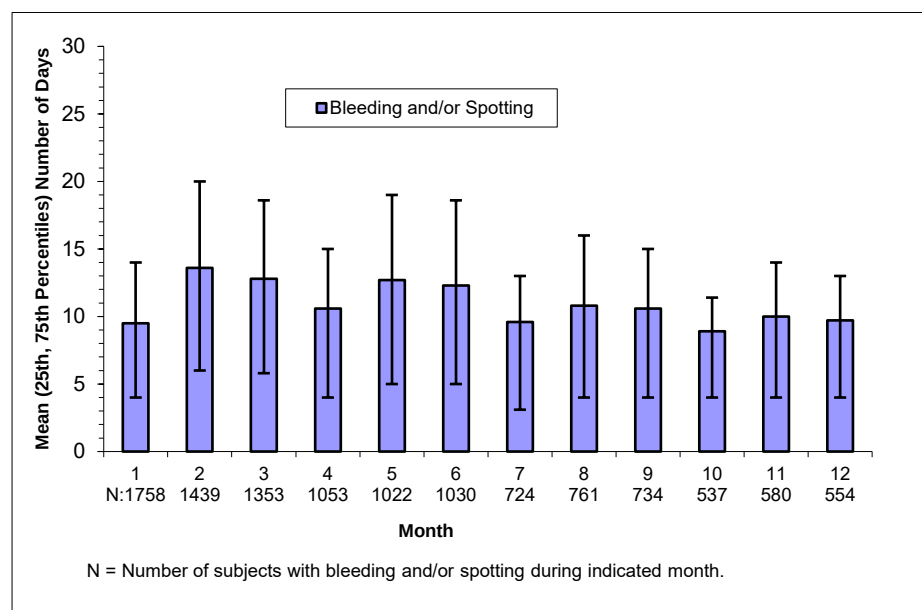
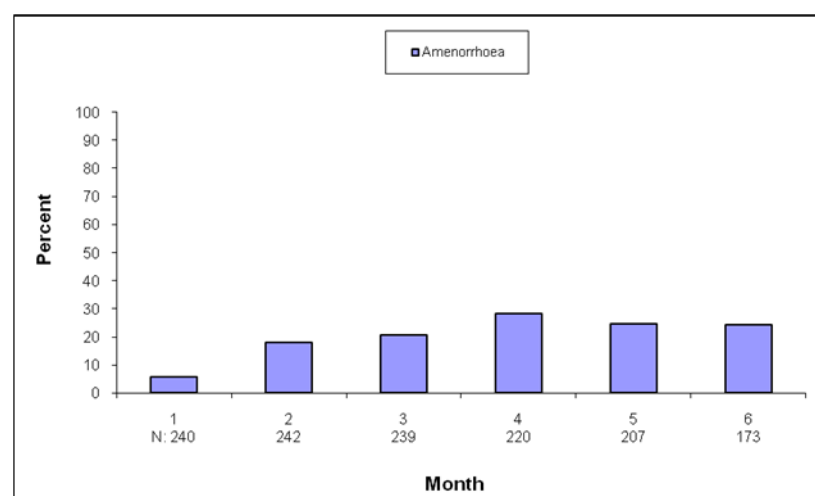


Figure 2. Percentages of SC MPA treated women with amenorrhoea per 30-day month in endometriosis studies (combined ITT population, N=289)



N = Number of subjects in analysis for indicated month.

Cancer risks

Long-term case-controlled surveillance of depot MPA IM 150 mg use for contraception found slight or no increased overall risk of breast cancer and no increased overall risk of ovarian, liver, or cervical cancer. There was a prolonged effect of reducing the risk of endometrial cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of IM MPA use.

The overall relative risk of breast cancer associated with the use of IM MPA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) has been associated with use of IM MPA in women whose first exposure to the drug was within the

previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2.0 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to IM MPA. The risk of breast cancer was comparable in similar groups of women who used either IM MPA or an oral contraceptive.

The Australian Institute of Health & Welfare reported that in 2006, a total of 12,614 Australian women were diagnosed with breast cancer. Across Australia, on average, 35 females were diagnosed with breast cancer each day in 2006. Overall, in 2006, more than two in three (69%) breast cancers in women were diagnosed in those aged 40 to 69 years, while one in four (25%) were diagnosed in those aged 70 and over. Based on data for 2006, 1 in 11 women will be diagnosed with breast cancer before the age of 75. By 2015, the number of new breast cancer cases among women is projected to be 22% higher than in 2006, with an estimated 15,409 women expected to be diagnosed with breast cancer. The age-standardised rate of breast cancer incidence stood at 112 (per 100,000 females) in 2006. A relative risk of 2.19 thus increases the possible risk from 112 to 245 cases per 100,000 women. The attributable risk, therefore, is 133 per 100,000 women per year.

It is important to inform patients that users of all hormonal contraceptives appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of hormonal contraceptives, but that this has to be weighed up against the known benefits.

The overall, non-significant relative rate of invasive squamous cell cervical cancer in women who ever used IM MPA was estimated at 1.11 (95% CI 0.95-1.28). A statistically insignificant increase in relative risk estimates of invasive squamous cell cervical cancer has been associated with the use of IM MPA in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Anaphylaxis and anaphylactoid reaction

Serious anaphylactic reactions have occasionally been reported in patients treated with IM MPA. If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Thromboembolic disorders

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient who develops an event such as pulmonary embolism, cerebrovascular disease or retinal thrombosis, while undergoing therapy with SC MPA, should not be readministered the drug. Women with a prior history of thromboembolic disorders have not been studied in clinical trials and no information is available that would support the safety of SC MPA use in this population (see Section 4.3 Contraindications).

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Weight changes

Weight changes are common but unpredictable. In the phase 3 studies body weight was followed over 12 months. Half (50%) of the women remained within 2.2 kg of their initial body weight. 12% of women lost more than 2.2 kg, and 38% of women gained more than 2.3 kg.

Weight gain increased with increasing treatment duration with a mean weight gain of 1.2 kg at 12 months and 4.5 kg at 3 years. The amount of weight gain observed for SC MPA subjects was comparable to that of IM MPA subjects.

Return of ovulation

Following a single dose of SC MPA 104 mg, the cumulative rate of return to ovulation as measured by plasma progesterone, was 97.4% (38/39 patients) by one year after administration. After the 14-week therapeutic window, the earliest return to ovulation was one week, the maximum time was >1 year, and the median time to ovulation was 30 weeks. The majority of women in the study (51.3%) ovulated between 28 and 36 weeks after the therapeutic window, while 30.6% ovulated before 28 weeks and 17.9% ovulated after 36 weeks. Women should be counselled that there is a potential for delay in return to ovulation following use of the method, regardless of the duration of use. It is recognised, however, that amenorrhoea and/or irregular menstruation upon discontinuation of hormonal contraception may be due to an underlying disorder associated with menstrual irregularity especially polycystic ovarian syndrome.

Sexually transmitted infections

Women should be counselled that DMPA injectable suspension does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) but equally, DMPA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Depression

Patients with a history of treatment for clinical depression should be carefully monitored while receiving SC MPA.

Injection site reactions

In 5 clinical studies of SC MPA 104 mg involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients receiving progestogens. For this reason, diabetic patients should be carefully observed while receiving progestogen therapy.

Liver function

If jaundice or any other liver abnormality develops in any woman receiving SC MPA, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the physician has determined that SC MPA did not cause the abnormality.

Use in the elderly

SAYANA is intended for use in women of childbearing potential. Studies with SC MPA in geriatric women have not been conducted.

Paediatric use

SAYANA is not indicated before menarche. Use of SC MPA is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for post-menarchal adolescents and adult women.

Effects on laboratory tests

The pathologist should be advised of progestogen therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestogen therapy:

- plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol)
- plasma and urinary gonadotropin levels are decreased (e.g., LH, FSH)
- SHBG concentrations are decreased
- T₃-uptake values may decrease

There may be small changes in coagulation factors. Sulfobromophthalein and other liver function test values may be increased slightly. There may be small changes in lipid profiles.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed with SAYANA.

Aminoglutethimide administered concomitantly with SC MPA may significantly decrease the serum concentration of MPA. SAYANA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Interactions with other medical treatments (including oral anticoagulants) have rarely been reported, but causality has not been determined. The possibility of interactions should be borne in mind in patients receiving concurrent treatment with other drugs.

The clearance of MPA is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect kinetics of MPA. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4. Special warnings and precautions for use – Return of ovulation.

Use in pregnancy – Pregnancy Category D

SAYANA is contraindicated in women who are pregnant. Studies in animals have shown teratogenicity and fetotoxicity with progestogens, including MPA. In addition, high doses of progestogens can cause masculinisation of the female fetus in animals and several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses in humans. If SAYANA is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be warned of the potential hazard to the fetus.

Accidental pregnancy

Infants from unintentional pregnancies that occurred 1 to 2 months after IM injection of 150 mg MPA may be at an increased risk of low birth weight. The attributable risk is low because pregnancies while on MPA injection 150 mg IM are uncommon.

Children exposed to MPA *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Ectopic pregnancy

As with all forms of hormonal contraception, health-care providers should be alert to the possibility of an ectopic pregnancy among women using SC MPA who become pregnant or complain of severe abdominal pain.

Use in lactation

Low detectable amounts of drug have been identified in the milk of mothers receiving MPA. In nursing mothers treated with MPA injection 150 mg IM, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to MPA from breast milk

have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

4.7 Effects on ability to drive and use machines

SAYANA has no influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

In five clinical studies of SC MPA involving 2,325 women (282 treated for up to 6 months, 1,780 treated for up to 1 year and 263 treated for up to 2 years), 9% of women discontinued treatment for adverse reactions. Among these 212 women, the most common reasons for discontinuation were:

- uterine bleeding irregularities (35%, n=75)
- increased weight (18%, n=39)
- decreased libido (11%, n=23)
- acne (10%, n=21)
- injection site reactions (6%, n=12).

Adverse reactions reported by 5% or more of all women in these clinical trials included:

- headache (9%)
- metrorrhagia (7%)
- increased weight (6%)
- amenorrhoea (6%)
- injection site reactions (5%).

Adverse reactions reported by 1% to <5% of all women in these clinical trials included:

General disorders and administrative site conditions: fatigue, injection site pain.

Gastrointestinal disorders: abdominal distention, abdominal pain, diarrhoea, nausea.

Infections and infestations: bronchitis, influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, vaginal candidiasis, vaginitis, vaginitis bacterial.

Investigations: abnormal cervix smear.

Musculoskeletal, connective tissue, and bone disorders: arthralgia, back pain, limb pain.

Nervous system disorders: dizziness, insomnia.

Psychiatric disorders: anxiety, depression, irritability, decreased libido.

Reproductive system and breast disorders: breast pain, breast tenderness, menometrorrhagia, menorrhagia, menstruation irregular, uterine haemorrhage, vaginal haemorrhage.

Skin and subcutaneous tissue disorders: acne.

Vascular disorders: hot flushes.

The events listed in Table 2 and 3 have been associated with the use of SC MPA for contraception and endometriosis-associated pain respectively.

Table 2. Events associated with the use of SC MPA for contraception

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Appetite decrease, Appetite increase, fluid retention, weight fluctuation
Psychiatric disorders	Anxiety, insomnia, anorgasmia, depression, emotional disorder, libido decreased, affective disorder, hypersomnia, irritability
Nervous system disorders	Headache, dizziness, migraine, formication
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hot flushes, hypertension, varicose veins
Gastrointestinal disorders	Abdominal pain, abdominal distension, nausea
Skin and subcutaneous tissue disorders	Hirsutism, acne, chloasma, dermatitis, ecchymosis, rash, alopecia
Musculoskeletal and connective tissue disorders	Back pain, muscle spasm, pain in extremity, polyarthralgia
Reproductive system and breast disorders	Amenorrhoea, breast pain, breast tenderness, metrorrhagia, menometrorrhagia, menorrhagia, vaginal discharge, vulvovaginal dryness, dysmenorrhea, change in breast size, dyspareunia, ovarian cyst, pelvic pain, premenstrual syndrome, uterine haemorrhage, vaginal haemorrhage
General disorders and administration site conditions	Fatigue, injection site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy)
Investigations	Abnormal liver enzymes, cervical smear abnormal

Table 3. Events associated with the use of SC MPA for endometriosis-associated pain

MedDRA SOC	Event
Infections and infestations	Vaginitis
Metabolism and nutrition disorders	Weight fluctuation
Psychiatric disorders	Anxiety, depression, insomnia, irritability, libido decreased, affective disorder
Nervous system disorders	Dizziness, formication, headache, hypersomnia, migraine, paresthesia
Cardiac disorders	Palpitations
Vascular disorders	Hot flushes
Gastrointestinal disorders	Abdominal distension, nausea
Skin and subcutaneous tissue disorders	Acne, alopecia, dermatitis
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, polyarthralgia

MedDRA SOC	Event
Reproductive system and breast disorders	Breast pain, breast tenderness, galactorrhoea, metrorrhagia, menorrhagia, ovarian cyst, pelvic pain, dysfunctional uterine bleeding (irregular, increase, decrease, spotting), vaginal haemorrhage, vulvovaginal dryness
General disorders and administration site conditions	Injection-site reactions (such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, lipodystrophy), fatigue

From clinical trial data on SC MPA use versus leuprolide use in endometriosis, the incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population) is shown in Table 4 below.

Table 4. Incidence of drug related AEs reported by $\geq 1\%$ of patients in the SC MPA group (ITT population)

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Ear and labyrinth disorders	2	1.3		
Vertigo NEC	2	1.3		
Gastrointestinal disorders	21	13.8	10	7.0
Dry mouth	2	1.3		
Gastritis NOS	2	1.3		
Nausea	17	11.2	10	7.0
Vomiting NOS	2	1.3		
General disorders and administration site conditions	6	3.9	3	2.1
Pyrexia	2	1.3		
Infections and infestations	5	3.3	4	2.8
Vaginitis	3	2.0	4	2.8
Investigations	4	2.6	6	4.2
Weight increased	3	2.0	4	2.8
Musculoskeletal, connective tissue and bone disorders	6	3.9	9	6.3
Arthralgia	3	2.0	3	2.1
Myalgia	2	1.3	2	1.4
Nervous system disorders	19	12.5	17	11.9
Formication	2	1.3		
Headache NOS	5	3.3	9	6.3
Headache NOS aggravated	2	1.3	1	0.7
Hypersomnia	7	4.6	3	2.1
Psychiatric disorders	14	9.2	9	6.3
Depression NEC	2	1.3		
Irritability	2	1.3	1	0.7
Libido decreased	6	3.9	6	4.2
Reproductive system and breast disorders	47	30.9	15	10.5
Breast disorder NOS	2	1.3		

Adverse Event ++	DMPA-SC (N=153)		Leuprolide (N=146)	
	n	%	n	%
Breast engorgement	2	1.3	1	0.7
Breast pain	8	5.3	5	3.5
Breast tenderness	4	2.6		
Intermenstrual bleeding	19	12.5	1	0.7
Menorrhagia	2	1.3	1	0.7
Menstruation irregular	2	1.3		
Uterine haemorrhage	7	4.6	1	0.7
Vaginal haemorrhage	5	3.3		
Skin & subcutaneous tissue disorders	9	5.9	6	4.2
Acne NOS	2	1.3	1	0.7
Dermatitis acneiform	2	1.3		
Vascular disorders	9	5.9	24	16.8
Hot flushes NOS	9	5.9	24	16.8

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

%=(n/Total Reported)*100, ++ Version 2.3 of the MedDRA Dictionary was used.

Protocol 839-FEH-0012-270: Endometriosis Study of DMPA-SC in Europe, Latin America, and Asia.

The following events have been associated with the use of progestogens including medroxyprogesterone:

Cardiac disorders: palpitations, myocardial infarction, congestive heart failure.

Endocrine disorders: Cushingoid syndrome, prolonged anovulation

Eye disorders: retinal thrombosis, visual impairment, diabetic cataract.

Gastrointestinal disorders: nausea, constipation, diarrhoea, dry mouth, vomiting.

General disorders and administration site conditions: hyperpyrexia, injection site reactions, arthralgia, malaise.

Hepatobiliary disorders: liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Investigations: decreased glucose tolerance, bone mineral density decreased, weight increased, blood pressure increased, increases in white cell, increases in platelet counts.

Immune system disorders: anaphylactic reaction, anaphylactoid reactions, angioedema.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia.

Nervous system disorders: somnolence, fatigue, dizziness, headache, tremor, loss of concentration, cerebral infraction.

Psychiatric disorders: nervousness, insomnia, depression, confusion, euphoria, changes in libido.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: breast pain, breast tenderness, galactorrhoea, changes in the position of the transformation zone and in secretions, cervical erosions.

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritus, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Please refer to the DEPO-PROVERA or DEPO-RALOVERA product information for additional adverse events that have been noted with the IM formulation.

Post-marketing experience

The following reactions have been reported with DEPO-PROVERA and DEPO-RALOVERA intramuscular injection and may occur with use of SC MPA:

Blood and lymphatic system disorders: anaemia, blood dyscrasia.

Cardiac disorders: tachycardia.

Endocrine disorders: prolonged anovulation.

Gastrointestinal disorders: gastrointestinal disorders, rectal bleeding.

General disorders and administration site conditions: asthenia, axillary swelling, chills, chest pain, fever, excessive thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: drug hypersensitivity, angioedema.

Infections and infestations: genitourinary tract infections.

Investigations: decreased glucose tolerance.

Musculoskeletal, connective tissue, and bone disorders: bone mineral density decreased, scleroderma.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): breast cancer, cervical cancer.

Nervous system disorders: convulsions, facial palsy, fainting, paralysis, paresthesia, somnolence.

Psychiatric disorders: increased libido, nervousness.

Reproductive system and breast disorders: breast lumps, galactorrhea, nipple discharge or bleeding, oligomenorrhea, prevention of lactation, unexpected pregnancy, uterine hyperplasia, vaginal cyst.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, dysphonia, pulmonary embolism.

Skin and subcutaneous tissue disorders: dry skin, skin odour abnormal, chloasma, pruritus, urticaria.

Vascular disorders: deep vein thrombosis, thrombophlebitis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis, including osteoporotic fractures, reported in patients taking IM MPA.

There have been post-marketing reports of lipodystrophy acquired.

Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness and injection site discolouration were identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No serious medical effects have been reported in association with overdosage of IM MPA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for any potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MPA is an analogue of 17 α -hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects.

SAYANA suspension for subcutaneous(SC) injection, when administered at 104 mg/0.65 mL to women every 3 months (12 to 14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

From a pharmacodynamic perspective, the duration of ovulation suppression depends upon maintaining therapeutic MPA concentrations throughout the 13 week dosing interval.

Suppression of serum estradiol concentrations and a possible direct action of MPA on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

Clinical trials

Contraception studies

In three clinical studies, no pregnancies were detected among 2,042 women using SC MPA for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use. Since no pregnancies occurred in the studies, it was

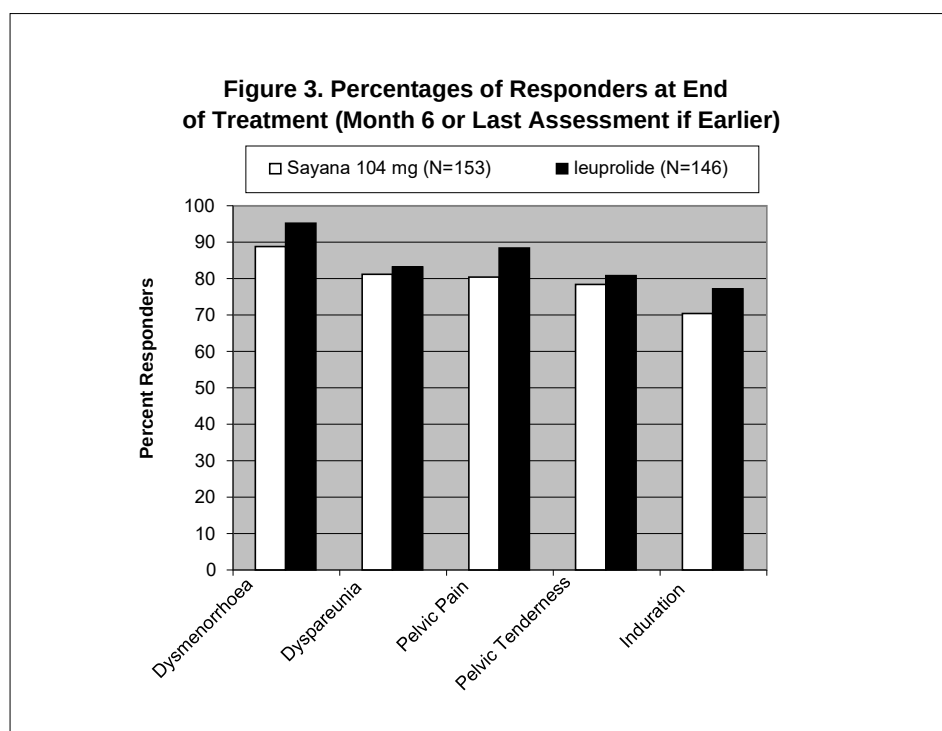
not methodologically appropriate to calculate a theoretical upper limit for the Pearl Index was 0.20 pregnancies per 100 women-years of use.

Endometriosis studies

The efficacy of SC MPA in the reduction of endometriosis-associated pain in women with the signs and symptoms of endometriosis was demonstrated in a randomised, evaluator-blinded (single-blinded), multicentre, phase 3 efficacy and safety study comparing SC MPA and leuprolide. Patients participated in the study for up to 18 months: 6 months on treatment with SC MPA (104 mg every 3 months) or leuprolide (11.25 mg, every 3 months or 3.75 mg every month) and 12 months of follow-up with no treatment given. The study assessed 299 women with recently diagnosed endometriosis, as well as women having persistent or recurrent symptoms of endometriosis who had not received drug treatment for at least 3 months. In all patients, endometriosis was confirmed using laparoscopy and/or histopathologic confirmation.

Reduction in pain was evaluated using a modified Biberoglu and Behrman scale that consisted of three patient-reported symptoms (dysmenorrhoea, dyspareunia, and pelvic pain not related to menses) and two signs (pelvic tenderness and induration). For each category, a favourable response was defined as improvement of at least 1 unit (severity was assessed on a scale of 0 to 3) relative to baseline score.

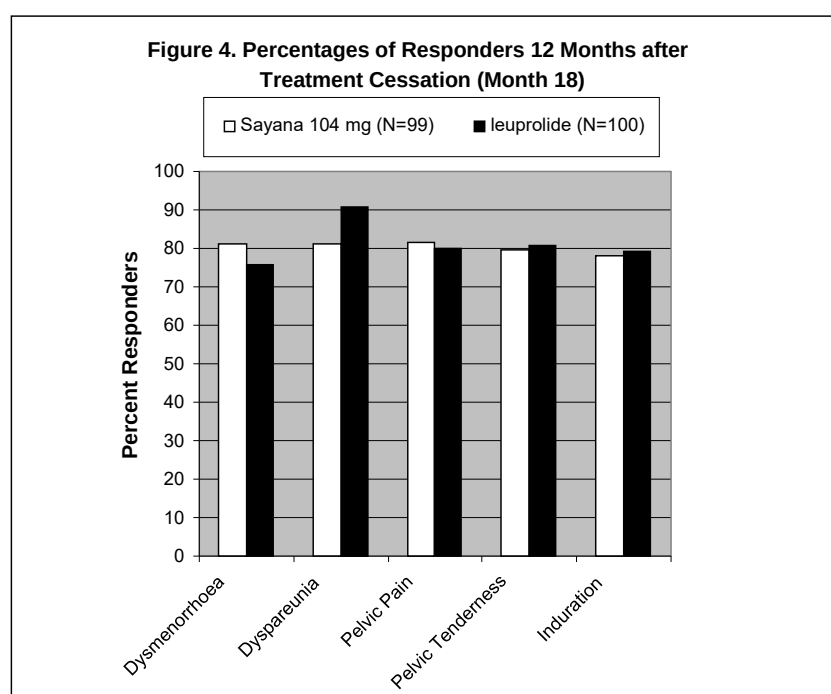
The primary endpoint, for each symptom or sign, was the % of patients in each treatment group who showed an improvement of 1 point or more; the difference (% of SAYANA patients improved minus % of leuprolide patients improved) was calculated. The efficacy of leuprolide versus placebo was not considered in designing the criterion for clinical equivalence of the primary endpoint. According to the statistical analysis plan, clinical equivalence of SAYANA to leuprolide was declared if the lower bound of the 96% confidence interval, for the difference, remained above -20% for at least 4 of the 5 symptoms/signs assessed. At End-of-Treatment (Month 6), the two treatments were clinically equivalent for all 5 symptoms/signs (Figure 3).



A composite score was also calculated as the sum of all 5 individual symptom/sign scores. The mean changes from baseline for the composite scores at 6 months were -6.3 for SC MPA patients and -7.3 for leuprolide on a scale of 0 to 15 points. The mean change for leuprolide was significantly different to the mean change for SC MPA, but both changes were significant versus baseline and met the pre-specified criterion for clinical significance, which was a decrease ≥ 4 points. In the clinical trial, treatment ended after six months; therefore, data on the benefits of longer treatment with SC MPA for endometriosis are not available.

Subjects recorded the occurrence and severity of hot flushes on a daily basis. Of the SC MPA users, 26.6% reported experiencing moderate or severe hot flushes at baseline, 35.9% at Month 3, and 29.0% at Month 6. Of the leuprolide users, 28.9% reported experiencing moderate or severe hot flushes at baseline, 71.0% at Month 3, and 71.2% at Month 6. No pregnancies were reported during the 6-month active treatment period with either SC MPA or leuprolide.

In a smaller study of similar design, there was one pregnancy reported amongst 136 women with endometriosis who received SC MPA, conception occurred at 72 days after injection.



Bone mineral density changes in adult women

In a controlled clinical study, adult women using MPA injection (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA injection (150 mg IM), there was progressive recovery of BMD toward baseline values during the 2-year post-therapy period. After 2 years off treatment, the BMD deficit had decreased to approximately 2.1% at the spine and hip. A longer duration of treatment was associated with a slower rate of BMD recovery.

A study comparing changes in BMD in women using SC MPA 104 mg with women using DEPO-PROVERA Injection 150 mg showed no significant differences in BMD loss between the two groups after two years of treatment. Mean percent changes in BMD in the SC MPA 104 mg group are listed in Table 5.

Table 5. Mean percent change from baseline in BMD in adult women using SC MPA 104 mg for contraception

	Time on treatment	Lumbar spine		Total hip		Femoral neck	
		n	mean % change (s.d.)	n	mean % change (s.d.)	n	mean % change (s.d.)
SC MPA 104 mg	12 months	166	-2.7 (2.6)	166	-1.7 (2.7)	166	-1.9 (3.6)
	24 months	106	-4.1 (2.9)	106	-3.5 (3.7)	106	-3.5 (4.5)

There were no pregnancies in the first year of treatment so the treatment failure pregnancy rate was 0%. In the second year, none of the SAYANA women became pregnant while one of the DEPO-PROVERA women became pregnant and was discontinued at 21 months.

BMD changes in adult women after six months of treatment for endometriosis

In two clinical studies of 573 adult women with endometriosis, the BMD effects of 6 months of SC MPA treatment were compared to 6 months of leuprolide treatment. Subjects were then observed, off therapy, for an additional 12 months (Table 6).

Table 6. Mean percent change from baseline in BMD: after 6 months on therapy with SC MPA or leuprolide and 6 and 12 months after stopping therapy

Time of measurement	Lumbar spine				Total hip			
	SC MPA		Leuprolide		SC MPA		Leuprolide	
	n	Mean % change	n	Mean % change	n	Mean % change	n	Mean % change
Month 6 of treatment (EOT)	208	-1.20	229	-4.10	207	-0.03	227	-1.83
6 months off treatment	168	-1.06	180	-2.75	169	-0.05	181	-1.59
12 months off treatment	124	-0.54	133	-1.48	125	0.39	134	-1.15

EOT = End of Treatment

BMD changes in adolescent females (12–18 years) after long-term treatment for contraception

An open-label non-randomised clinical study of MPA injectable (150 mg IM every 3 months for up to 240 weeks [4.6 years]) in adolescent females (12–18 years) for contraception also showed a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynaecologic age, race, BMD and other factors that influence the rate of acquisition of BMD, with the result that they differed with respect to these demographic factors.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued. In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively. The possibility of a change in risk for future fragility fracture arising from depot medroxyprogesterone acetate (DMPA) use remains to be investigated.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters following a single SC injection of MPA are shown in Table 7.

Table 7. Pharmacokinetic parameters after a single SC injection of MPA in healthy women (n=42)

	C_{max} (ng/mL)	T_{max} (day)	C_{91 (min)} (ng/mL)	AUC₀₋₉₁ (ng·day/mL)	AUC_{0-∞} (ng·day/mL)	t_{1/2} (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC₀₋₉₁ = area under the concentration-time curve over 91 days; t_{1/2} = terminal half-life; 1 nanogram = 10³ picogram.

Absorption

MPA absorption from the SC injection site is relatively prompt in terms of achieving therapeutic levels. Following a single SC injection of MPA, serum MPA concentrations reach ≥ 0.2 ng/mL within 24 hours. The mean T_{max} attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/mL with a mean C_{max} of 1.5 ng/mL after a single SC injection.

A direct bioequivalence study between the IM MPA formulation and SC MPA given subcutaneously at each of the two proposed sites has not been conducted.

Effect of injection site

MPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy.

Distribution

Plasma protein binding of MPA averages 86%. MPA binds primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolised in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (3 months) are generally below 0.5 ng/mL, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/non-linearity

Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the $C_{\min}$ and the SC dose of MPA appeared to be linear. The mean $C_{\max}$ did not change substantially with increasing dose.

Special populations

Race

No dose adjustment based on race is necessary. There were no apparent differences in the pharmacokinetics and/or dynamics of MPA after SC administration of SAYANA among the women of different races involved in the studies.

Effect of body weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2 to 46.0 kg/m²). The AUC₀₋₉₁ values for MPA were 68.5, 74.8, and 61.8 ng·day/mL in women with BMI categories of ≤ 25 kg/m², > 25 to ≤ 30 kg/m², and > 30 kg/m², respectively. The mean MPA $C_{\max}$ was 1.65 ng/mL in women with BMI ≤ 25 kg/m², 1.76 ng/mL in women with BMI >25 to ≤ 30 kg/m², and 1.40 ng/mL in women with BMI > 30 kg/m², respectively. The range of MPA trough ($C_{\min}$) concentrations and the half-lives were comparable for the 3 BMI groups.

Renal impairment

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of SC MPA.

Hepatic impairment

No clinical studies have evaluated the effect of hepatic disease on the disposition of SC MPA. However, steroid hormones may be poorly metabolised in patients with severe liver dysfunction (see Section 4.3 Contraindications).

5.3 Preclinical safety data

Genotoxicity

MPA was negative in assays for bacterial mutagenicity, DNA damage *in vitro* (Chinese hamster lung fibroblasts) and clastogenicity *in vivo* (rat micronucleus test).

Carcinogenicity

See Section 4.4 Special warnings and precautions for use – Cancer risks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each pre-filled syringe contains the following inactive ingredients: methyl hydroxybenzoate and propyl hydroxybenzoate (added as resuspending agents), sodium chloride, macrogol 3350, polysorbate 80, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dodecahydrate, methionine, povidone, water for injections and sodium hydroxide and/or hydrochloric acid (added for pH adjustment).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

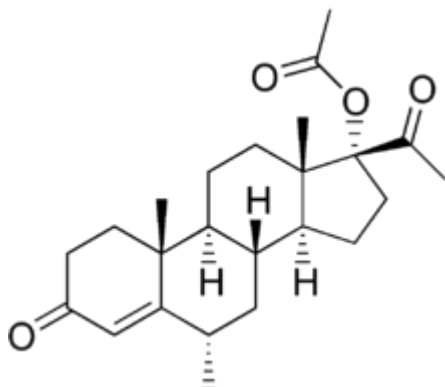
SAYANA 104 mg/0.65 mL (medroxyprogesterone acetate) suspension for subcutaneous injection is supplied as a single dose, pre-filled syringe packaged with a 26-gauge, 3/8 inch needle that is included separately.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Non-proprietary name: medroxyprogesterone acetate.

Chemical name: 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate

Molecular formula: C₂₄H₃₄O₄

Molecular weight: 386.5.

CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 July 2011

10. DATE OF REVISION

DD Month YYYY

® Registered Trademark.

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
All	Minor editorial changes

AUSTRALIAN PRODUCT INFORMATION – PROVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA tablets contain 2.5 mg, 5 mg, 10 mg, 100 mg, 200 mg, 250 mg or 500 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect

Lactose monohydrate (2.5, 5 and 10 mg tablets)

Sodium benzoate (100, 200, 250 and 500 mg tablets)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

100 mg tablets: white, scored, marked U467.

200 mg tablets: white, scored, marked U320.

250 mg tablets: white, scored, marked U403.

500 mg tablets: white, capsule-shaped, marked UPJOHN 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with MPA.

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use**Physical examination**

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine

and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use PROVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of PROVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of PROVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

PROVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than 70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should

consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

PROVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of PROVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the

control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to PROVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

PROVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 2.5, 5, and 10 mg tablets:

calcium stearate
indigo carmine (5 mg tablet)
sunset yellow FCF (2.5 mg tablet)
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose

PROVERA 100, 200, 250, and 500 mg tablets:

docusate sodium
gelatin
isopropyl alcohol
macrogol 400
magnesium stearate
maize starch
microcrystalline cellulose
purified water
sodium benzoate
sodium starch glycollate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PROVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

100 mg tablets: blister packs of 10 and 100 tablets.

200 mg tablets: blister packs of 10 and 60 tablets.

250 mg tablets: blister packs of 10 and 60 tablets.

500 mg tablets: blister packs of 10, 30 and 60 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

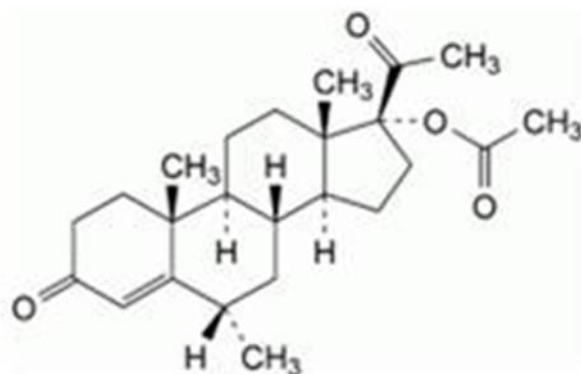
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

10. DATE OF REVISION

DD Month YYYY

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
1, 4.1	Minor editorial changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

AUSTRALIAN PRODUCT INFORMATION – RALOVERA[®] (MEDROXYPROGESTERONE ACETATE) TABLETS

1. NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RALOVERA tablets contain 2.5 mg, 5 mg or 10 mg medroxyprogesterone acetate as the active ingredient.

Excipient(s) with known effect

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

2.5 mg tablets: orange, circular, scored on one side, marked U64 on the other side.

5 mg tablets: pale blue, circular, scored on one side and marked 286 on both sides of the score line, marked U on the other side.

10 mg tablets: white, circular, scored on one side, marked UPJOHN 50 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

Palliative treatment of recurrent and/or metastatic breast or renal cell cancer and of inoperable recurrent or metastatic endometrial carcinoma.

Endometriosis

For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with MPA.

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy (HRT) should only be used in non-hysterectomised women (see Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Dosage

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy[#]

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

[#] Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without re-examining the patient.

4.3 Contraindications

RALOVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or to any of the excipients in the tablet
- known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

4.4 Special warnings and precautions for use

Physical examination

The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with RALOVERA for recurrent endometrial, breast or renal cancer.

Thromboembolic disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur, the drug should be discontinued immediately.

Meningioma

Meningiomas have been reported following long-term administration of progestins, including MPA. MPA should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Ocular disorders

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilloedema, or retinal vascular lesions, medication should be withdrawn.

Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however, at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen regimen in post-menopausal women have reported an increased risk of

several disorders including cardiovascular diseases (e.g., coronary heart disease and stroke), breast cancer, and venous thromboembolism.

Breast cancer

Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of HRT on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen therapy in post-menopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in post-menopausal women is not generally appropriate for long-term use and should not be prescribed for longer than 6 months without re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of RALOVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1.2 years at the lumbar spine and 4.6 years at the total hip and femoral neck (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see Section 5.1 Pharmacodynamic properties - Clinical trials). A large observational study of female contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

An evaluation of BMD may be appropriate in some patients who use RALOVERA long term. It is recommended that all patients have adequate calcium and Vitamin D intake.

Fluid retention

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, or cardiac or renal dysfunction, require careful observation.

Breakthrough bleeding

Breakthrough bleeding is likely to occur in patients being treated for endometriosis. No other hormonal intervention is recommended for managing this bleeding. Non-functional causes should also be borne in mind and in cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. This fact should be borne in mind when treating all patients and for this reason diabetic patients should be carefully observed while receiving progestogen therapy.

CNS disorders and convulsions

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patient age

The age of the patient constitutes no absolute limiting factor although treatment with progestogens may mask the onset of the climacteric.

Pathology tests

The pathologist should be advised of progestogens therapy when relevant specimens are submitted.

Weight changes

Weight gain may be associated with the use of RALOVERA. Caution should therefore be exercised in treating any patient with a pre-existing condition that may be adversely affected by weight gain.

General

The high doses of RALOVERA used in the treatment of cancer patients may, in some cases, produce Cushingoid symptoms, e.g., moon facies, fluid retention, glucose tolerance and blood pressure elevation.

Use in hepatic impairment

RALOVERA is contraindicated in patients with markedly impaired liver function (see Section 4.3 Contraindications).

Use in the elderly

A higher incidence of probable dementia in women aged 65 years and older has been reported during treatment with a HRT regimen of conjugated estrogens and MPA. Eighty-five percent of cases of probable dementia occurred in the subgroup of women (54%) that were older than

70 years of age. Use of hormone therapy to prevent dementia or mild cognitive impairment in women 65 years or older is not recommended.

Paediatric use

No data available.

Effects on laboratory tests

The following laboratory tests may be affected by the use of RALOVERA:

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test – the use of MPA in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex to respond to adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with RALOVERA may significantly depress the bioavailability of MPA. Users of high-dose MPA should be warned about the possibility of decreased efficacy with the use of aminoglutethimide.

MPA is metabolised *in vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur which may result in compromised efficacy. Co-administration with CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

4.6 Fertility, pregnancy and lactation

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Use in pregnancy – Pregnancy Category D

RALOVERA TABLETS ARE NOT TO BE USED AS A TEST FOR PREGNANCY OR WHERE PREGNANCY IS SUSPECTED.

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus (see Section 4.3 Contraindications).

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include dizziness, somnolence and visual impairment which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The following events have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on RALOVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: urticaria, pruritis, rash, acne, hirsutism, alopecia, hyperhidrosis.

Vascular disorders: embolism and thrombosis, thrombophlebitis.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. MPA induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animal tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Human

MPA is a progestational agent. When administered in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA may inhibit gonadotrophin production, which in turn prevents follicular maturation and ovulation.

Like progesterone, MPA is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more), corticoid-like activity may be manifest.

Clinical trials

Bone mineral density changes

There are no studies on the bone mineral density (BMD) effects of RALOVERA.

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of MPA IM injection there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from

baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and total hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life. See Section 4.4 Special warnings and precautions for use.

5.2 Pharmacokinetic properties

RALOVERA is an orally active progestational steroid having an apparent half-life of about 30 hours.

MPA is rapidly absorbed after oral administration. There is high interindividual variability in serum levels after standard doses given by either route of administration.

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were 2 high dose animals that developed breast malignancies.

Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

No uterine or breast abnormalities were revealed in the rat after 2 years.

The relevance of any of these findings with respect to humans has not been established.

Animal toxicology

Acute toxicity: The oral LD₅₀ of MPA was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD₅₀ in the mouse was 6985 mg/kg.

Subacute and chronic toxicity: MPA administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium stearate
lactose monohydrate
liquid paraffin
maize starch
purified talc
sucrose
sunset yellow FCF (2.5 mg tablet)
indigo carmine (5 mg tablet)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

RALOVERA tablets are available in PVC/AL blister packs. The 10 mg tablets are also available in HDPE bottles.

2.5 mg tablets: blister packs of 28 and 56 tablets.

5 mg tablets: blister packs of 28 and 56 tablets.

10 mg tablets: blister packs of 15 and 30 tablets and bottles of 100 tablets.

+ Not all strengths and pack sizes may be available.

6.6 Special precautions for disposal

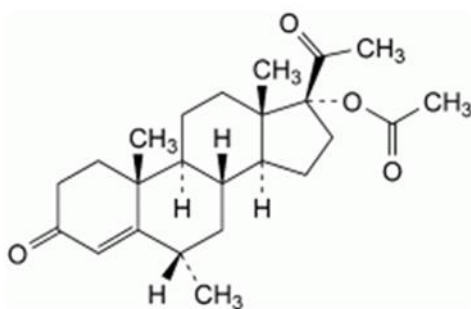
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate, and its structural formula is as follows:



CAS number

71-58-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 October 1993

10. DATE OF REVISION

DD Month YYYY

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
1, 4.1	Minor editorial changes
4.4	Addition of information regarding meningioma
8	Update to sponsor website address

From: s22
To: s22 ; s22
Cc: s22 ; s22
Subject: RE: Request for input - due 11 am Thursday 19 December - MEDIA FOR ACTION - ABC - Depo-Provera [SEC=OFFICIAL]
Date: Wednesday, 18 December 2024 3:09:04 PM
Attachments: [image002.png](#)
[image006.png](#)
[image007.png](#)
[image008.png](#)

Dear s22

Please find the responses to the enquiries from the PMAB perspective below. This enquiry would likely benefit from input from PB, as there was a medicine safety notification submitted to MSSI on 26 October 2023 which notes the intention of the Sponsor to add this signal as a new warning in Section 4.3 of the PI ([D23-3879031](#)) s22
s22
s22
s22

I have provided my response in purple italic font below and noted where a response from PB may be required.

Please let me know if you need anything further,

Kind regards

s22

I note the TGA updated its Product Information for Depo-Provera in February in response to Pfizer's update – was this the first time it had considered adding meningioma risk? Why not sooner given the increasing body of evidence linking hormones to these hormone sensitive tumours?

The proposed addition of Meningioma as a warning in Section 4.3 of the PI for Depo-Provera was submitted to the TGA by the Sponsor, Pfizer Australia Pty Ltd, and was approved on 26 February 2024. This new information was then published as part of the March 2024 Medicines Safety Update on the TGA website. Sponsors are obligated as part of their conditions of registration to update product information with new safety information as it becomes available.

This question may benefit from a further response from PB as PMAB only evaluates sponsor-initiated safety changes to PIs and does not evaluate signals.

The meningioma risk is in the Product Information but not in the Consumer Medicine Information – why not?

Regarding the Consumer Medicines Information (CMI) document, it is the sponsor's responsibility to ensure the CMI is consistent with the product information (PI), as per TGA regulations. You may wish to contact the sponsor of DEPO-PROVERA, Pfizer Australia Pty Ltd, to ask about updates to the CMI.

Depo-Provera is recommended for two years of use at a time because of its risk of osteoporosis – we’ve heard from women who’ve been on it much longer than that with no bone mineral density tests, one developed osteoporosis in her forties. What measures does TGA take to ensure doctors are aware of these kinds of risks and pass them onto patients. In the case of Depo-Provera many women have told us that because it’s an injection they were never given a box or leaflet by practice nurses, so never saw or heard about risks.

The safety information for medicines is presented in the PI for the medicine, and in the CMI, for which the sponsor is responsible for. Medicines Safety updates are also regularly published on the TGA website, and the notification for Depo-Provera can be found in the March 2024 update here: <https://www.tga.gov.au/news/safety-updates/product-information-safety-updates-march-2024>. The PI is one source of information for health professionals to assist with prescribing and dispensing. Further information is available in clinical resources and guidance.

Has TGA issued any warnings to doctors given the recent studies showing the five-fold increase in meningioma risk?

PMAB has no regulatory power to issue warnings to doctors, perhaps PB would be best placed to answer this question.

While I note the hormone, medroxyprogesterone acetate, has uses treating other conditions like endometriosis, breast and endometrial cancer is the TGA going to reconsider this medicine’s status given the increased risk or such a serious side effect from the high-dose Depo-Provera shot?

A question for PB to answer?

From: s22 @health.gov.au>
Sent: Wednesday, 18 December 2024 9:07 AM
To: s22 @Health.gov.au>; s22 @Health.gov.au>
Cc: s22 @Health.gov.au>; s22 @health.gov.au>
Subject: Request for input - due 11 am Thursday 19 December - MEDIA FOR ACTION - ABC - Depo-Provera [SEC=OFFICIAL]

Good morning s22

Seeking PES’ input regarding an SRR made to the PI for Depo-Provera in February this year, please, in response to media enquiry.

I have added some standard words to the proposed response – more than happy for you to revise/edit as required.

This one is not due until tomorrow afternoon, so it would be great if you could send a draft back to me by **11 am tomorrow, Thursday 19 December**, please.

Thanks,
s22

Query:

I note the TGA updated its Product Information for Depo-Provera in February in response to Pfizer's update – was this the first time it had considered adding meningioma risk? Why not sooner given the increasing body of evidence linking hormones to these hormone sensitive tumours?

The meningioma risk is in the Product Information but not in the Consumer Medicine Information – why not?

Depo-Provera is recommended for two years of use at a time because of its risk of osteoporosis – we've heard from women who've been on it much longer than that with no bone mineral density tests, one developed osteoporosis in her forties. What measures does TGA take to ensure doctors are aware of these kinds of risks and pass them onto patients. In the case of Depo-Provera many women have told us that because it's an injection they were never given a box or leaflet by practice nurses, so never saw or heard about risks.

Has TGA issued any warnings to doctors given the recent studies showing the five-fold increase in meningioma risk?

While I note the hormone, medroxyprogesterone acetate, has uses treating other conditions like endometriosis, breast and endometrial cancer is the TGA going to reconsider this medicine's status given the increased risk or such a serious side effect from the high-dose Depo-Provera shot?

Proposed response:

- Sponsors have obligations to ensure the PI is up to date, including updates to safety information as it becomes available.
- The information in a PI document has been written by the medicine sponsor and is approved by the TGA.
- The TGA may request that a sponsor update the PI if a safety issue is identified via adverse event reporting or if there is inconsistency between risks detailed in the Australian PI and overseas product information documents.
- s22 [REDACTED]
- The PI is one source of information for health professionals to assist with prescribing and dispensing. Further information is available in clinical resources and guidance.
- Information regarding specific risks associated with the medicines in your question is accessible via online search engines, relevant journals and publicly available clinical resources.
- With regard to the Consumer Medicines Information (CMI) document, it is the sponsor's responsibility to ensure the CMI is consistent with the product's PI, as per TGA regulations. You may wish to contact the sponsor of DEPO-PROVERA, Pfizer Australia Pty Ltd, to ask about updates to the CMI.

From: s22 [REDACTED] <[REDACTED]@health.gov.au>

Sent: Wednesday, 18 December 2024 8:42 AM

To: SIMPSON, Andrew <Andrew.Simpson@health.gov.au>

Cc: s22 [REDACTED] <[REDACTED]@tga.gov.au>; s22 [REDACTED]

s22 [REDACTED]@health.gov.au>; s22 [REDACTED]@health.gov.au>; s22 [REDACTED]@health.gov.au>; HICKIE, Megan <Megan.Hickie@health.gov.au>; RUSSELL, Sophie <Sophie.Russell@health.gov.au>
Subject: MEDIA FOR ACTION: Due 4PM Thursday 19/12 - ABC - Depo-Provera [SEC=OFFICIAL]

Good morning Andrew,

Please see the below media request for your appropriate action.

FOR NOTING: PB has advised that this PI update was not approved by PB – they have advised us to check with PMAB if this is a sponsor-initiated updated processed?

-

MEDIA FOR ACTION (AS CLEARANCE)	
News Outlet	ABC
AS clearance by (time)	4PM Thursday, 19 December

Query:

I note the TGA updated its Product Information for Depo-Provera in February in response to Pfizer's update – was this the first time it had considered adding meningioma risk? Why not sooner given the increasing body of evidence linking hormones to these hormone sensitive tumours?

The meningioma risk is in the Product Information but not in the Consumer Medicine Information – why not?

Depo-Provera is recommended for two years of use at a time because of its risk of osteoporosis – we've heard from women who've been on it much longer than that with no bone mineral density tests, one developed osteoporosis in her forties. What measures does TGA take to ensure doctors are aware of these kinds of risks and pass them onto patients. In the case of Depo-Provera many women have told us that because it's an injection they were never given a box or leaflet by practice nurses, so never saw or heard about risks.

Has TGA issued any warnings to doctors given the recent studies showing the five-fold increase in meningioma risk?

While I note the hormone, medroxyprogesterone acetate, has uses treating other conditions like endometriosis, breast and endometrial cancer is the TGA going to reconsider this medicine's status given the increased risk or such a serious side effect from the high-dose Depo-Provera shot?

Proposed response:

Please note when drafting a media response, it should be a brief statement or 1-5 dot points that summarise/address the enquiry and/or argument. If further information (technical/policy/legislative) is required, please include it as background to provide context and help the journalist better understand the issue.

Kind regards,

s22 [REDACTED]

**Media Officer – Parliamentary and Reporting Section
Regulatory Engagement Branch**

Regulatory Practice and Support Division | Health Products Regulation Group

Australian Government Department of Health and Aged Care

After hours: s22 [REDACTED] | E: s22 [REDACTED] @health.gov.au

Location: Fairbairn Office

PO Box 100, Woden ACT 2606, Australia

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From: HICKIE, Megan <Megan.Hickie@health.gov.au>

Sent: Tuesday, 17 December 2024 5:53 PM

To: s22 [REDACTED] @health.gov.au>

Cc: LARTER, Claire <Claire.Larter@health.gov.au>; RUSSELL, Sophie

<Sophie.Russell@health.gov.au>; s22 [REDACTED] @health.gov.au>; s22 [REDACTED]

s22 [REDACTED] @health.gov.au>; s22 [REDACTED] @tga.gov.au>;

s22 [REDACTED] @health.gov.au>

Subject: RE: MEDIA FOR ACTION: Due 4PM Thursday 19/12 - ABC - Depo-Provera [SEC=OFFICIAL]

Hi TGA Media,

This PI update was not approved by PB – would you mind checking with PMAB if this is a sponsor-initiated updated processed by that branch? If so, this response would be best placed with PMAB.

Many thanks,

Megan

Dr Megan Hickie BA MBBS DCH (she/her)
Principal Medical Adviser – Pharmacovigilance Branch

Medicines Regulation Division | Therapeutic Goods Administration

Pharmacovigilance Branch

Australian Government Department of Health and Aged Care

E: megan.hickie@health.gov.au

PO Box 100, Woden ACT 2606

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This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all of the legislative requirements are met.

From: s22 [REDACTED]@health.gov.au>
Sent: Tuesday, 17 December 2024 4:13 PM
To: LARTER, Claire <Claire.Larter@health.gov.au>
Cc: s22 [REDACTED]@tga.gov.au>; s22 [REDACTED]
s22 [REDACTED]@health.gov.au>; s22 [REDACTED]@health.gov.au>; s22 [REDACTED]
s22 [REDACTED]@health.gov.au>
Subject: MEDIA FOR ACTION: Due 4PM Thursday 19/12 - ABC - Depo-Provera [SEC=OFFICIAL]

Good afternoon Claire,

Please see the below media request for your appropriate action.

MEDIA FOR ACTION (AS CLEARANCE)	
News Outlet	ABC
AS clearance by (time)	4PM Thursday, 19 December

Query:

I note the TGA updated its Product Information for Depo-Provera in February in response to Pfizer's update – was this the first time it had considered adding meningioma risk? Why not sooner given the increasing body of evidence linking hormones to these hormone sensitive tumours?

The meningioma risk is in the Product Information but not in the Consumer Medicine Information – why not?

Depo-Provera is recommended for two years of use at a time because of its risk of osteoporosis – we've heard from women who've been on it much longer than that with no bone mineral density tests, one developed osteoporosis in her forties. What measures does TGA take to ensure doctors are aware of these kinds of risks and pass them onto patients. In the case of Depo-Provera many women have told us that because it's an injection they were never given a box or leaflet by practice nurses, so never saw or heard about risks.

Has TGA issued any warnings to doctors given the recent studies showing the five-fold increase in meningioma risk?

While I note the hormone, medroxyprogesterone acetate, has uses treating other conditions like endometriosis, breast and endometrial cancer is the TGA going to reconsider this medicine's status given the increased risk or such a serious side effect from the high-dose Depo-Provera shot?

Proposed response:

Please note when drafting a media response, it should be a brief statement or 1-5 dot points that summarise/address the enquiry and/or argument. If further information (technical/policy/legislative) is required, please include it as background to provide context and help the journalist better understand the issue.

Kind regards,

s22

**Media Officer – Parliamentary and Reporting Section
Regulatory Engagement Branch**

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care

After hours: s22 | E: s22@health.gov.au

Location: Fairbairn Office

PO Box 100, Woden ACT 2606, Australia

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From: News <news@health.gov.au>

Sent: Tuesday, 17 December 2024 4:08 PM

To: s22@health.gov.au

Cc: News <news@health.gov.au>

Subject: MEDIA ENQUIRY - Depo-Provera - Deadline 5pm Thursday [SEC=OFFICIAL]

Hi TGA,

Please see below for a media enquiry, deadline is 5pm Thursday.

Thanks,

s22

s22

Media and Events, Corporate Communication Branch

Australian Government, Department of Health and Aged Care

T: s22 | s22 E: news@health.gov.au

Unless stated otherwise, this information is provided on a background basis and should not be attributed.

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From: s22@abc.net.au

Sent: Tuesday, 17 December 2024 4:04 PM

To: News <news@health.gov.au>

Subject: Media Inquiry - TGA

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Hi 

Thanks for your time today.

As discussed, ABC news is looking into a piece about links between the Depo-Provera contraceptive injection and meningiomas – a type of benign brain tumour.

It follows a large-scale study published in the BMJ in March which is the largest to date but also comes on a rising body of research linking the high dose progesterone shot to the hormone sensitive brain tumours.

<https://www.bmj.com/content/384/bmj-2023-078078>

Questions

I note the TGA updated its Product Information for Depo-Provera in February in response to Pfizer's update – was this the first time it had considered adding meningioma risk? Why not sooner given the increasing body of evidence linking hormones to these hormone sensitive tumours?

The meningioma risk is in the Product Information but not in the Consumer Medicine Information – why not?

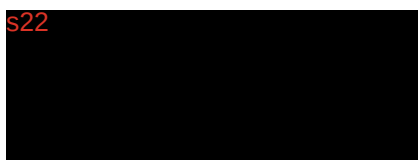
Depo-Provera is recommended for two years of use at a time because of its risk of osteoporosis – we've heard from women who've been on it much longer than that with no bone mineral density tests, one developed osteoporosis in her forties. What measures does TGA take to ensure doctors are aware of these kinds of risks and pass them onto patients. In the case of Depo-Provera many women have told us that because it's an injection they were never given a box or leaflet by practice nurses, so never saw or heard about risks.

Has TGA issued any warnings to doctors given the recent studies showing the five-fold increase in meningioma risk?

While I note the hormone, medroxyprogesterone acetate, has uses treating other conditions like endometriosis, breast and endometrial cancer is the TGA going to reconsider this medicine's status given the increased risk or such a serious side effect from the high-dose Depo-Provera shot?

It would be good to get a response by 5pm Thursday but let me know if you need more time.

Kind regards,


s22



s22 [REDACTED]@abc.net.au

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From: s22
 To: [Signal Investigation Coordinator](#)
 Cc: s22 ; s22 ; s22 ; s22 ; s22 ; s22
 Subject: RE: [EXTERNAL] Medicine safety notification: Pfizer Australia Pty Ltd : Medroxyprogesterone (Depo-Provera, Provera, Depo-Ralovera, Ralovera and Sayana) and Meningioma
 Date: Thursday, 26 October 2023 9:54:09 AM
 Attachments: [image001.png](#)
[23-0284_MEDROXYPROGESTERONE HTML-TRX-SMT-8482.pdf](#)

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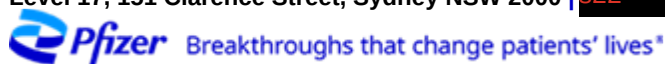
Dear TGA,

Please find attached the Pfizer's signal assessment.

Should you have any questions or require further information relating to this matter, please do not hesitate to contact me.

Kind regards

s22 | s22
 (Pronoun: She/Her)
Pfizer Australia Pty Ltd. | Drug Safety Unit
 Level 17, 151 Clarence Street, Sydney NSW 2000 | s22 | s22 [@pfizer.com](#)



I acknowledge and respect the Traditional Lands of all Aboriginal People. I acknowledge that Aboriginal People are the first people of this country. I pay my respects to all Elders past, present and future. I ask all those that walk, work and live on traditional Aboriginal Lands to be respectful of culture and traditions.

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From: s22 @health.gov.au s22 @health.gov.au>
 Sent: Thursday, 26 October 2023 9:52 AM
 To: s22 @pfizer.com>
 Subject: [EXTERNAL] Medicine safety notification: Pfizer Australia Pty Ltd : Medroxyprogesterone (Depo-Provera, Provera, Depo-Ralovera, Ralovera and Sayana) and Meningioma

Submitted on Thu, 2023-10-26 09:37

Submitted by: Anonymous

Remember, please reply to this email and attach relevant supporting documents if required.

Submitted values are:

Reporter details

Reporting sponsor

Pfizer Australia Pty Ltd

Reporters name

s22

Contact email address

s22@pfizer.com

Issue details

Safety issue

Medroxyprogesterone (Depo-Provera, Provera, Depo-Ralovera, Ralovera and Sayana) and Meningioma

Type of safety issue

OSI - Other safety issue

Date of local awareness by the sponsor (Day 0)

2023-09-26

Type of notification

Initial

Product details

Is your company the product innovator?

Yes

Product details

- **Product name:** DEPO-PROVERA medroxyprogesterone acetate 150 mg/mL aqueous suspension injection vial
ARTG no.: 12300
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA medroxyprogesterone acetate 100mg tablet
ARTG no.: 12331
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA medroxyprogesterone acetate 200mg tablet
ARTG no.: 12333
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes

- Product name:** PROVERA medroxyprogesterone acetate 250mg tablet
ARTG no.: 12334
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** PROVERA medroxyprogesterone acetate 500mg tablet
ARTG no.: 12336
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** PROVERA Medroxyprogesterone acetate 2.5mg tablet
ARTG no.: 42932
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** PROVERA Medroxyprogesterone acetate 5mg tablet
ARTG no.: 42933
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** PROVERA Medroxyprogesterone acetate 10mg tablet
ARTG no.: 42934
 : 46531
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** RALOVERA medroxyprogesterone acetate 10mg tablet
ARTG no.: 46532
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** RALOVERA medroxyprogesterone acetate 10mg tablet
ARTG no.: 46534
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- Product name:** SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe
ARTG no.: 167889
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: No
- Product name:** DEPO-PROVERA medroxyprogesterone ac

Issue source

Safety issue source

Comparable overseas regulator

Safety issue summary

PRAC requested a review of the signal of Meningioma on 18-May-2023. Review of the signal concluded on 26-Sep-2023 which confirmed the signal as an important potential risk. Notification of the signal from above country Pfizer colleagues was received 26-Sep-2023.

A literature search (Embase, BIOSIS Previews, Ovid MEDLINE(R), Google Scholar) for Risk AND (medroxyprogesterone OR MPA OR DMPA) AND meningioma.

A global safety data base search has been conducted for medicinal products containing medroxyprogesterone and all PTs that contain the word "meningioma", cumulatively through 10 May 2023.

Even though there are multiple literature sources discussing the influence of medroxyprogesterone in the development and growth of meningiomas, a definite sole association cannot be established, due to multiple other factors involved in the etiology of meningiomas (genetic, environmental, traumatic, etc). In the general population, according to the Central Brain Tumor Registry of the United States Statistical Report, of tumors diagnosed in the U.S. alone in 2012-2016, meningiomas were the most frequently reported overall histology (37.6%) of all primary central nervous system tumors with 33,560 cases projected in 2019. The average annual age-adjusted incidence rate was also highest for meningiomas (8.6 per 100,000 people) of all primary brain and spinal cord tumors.

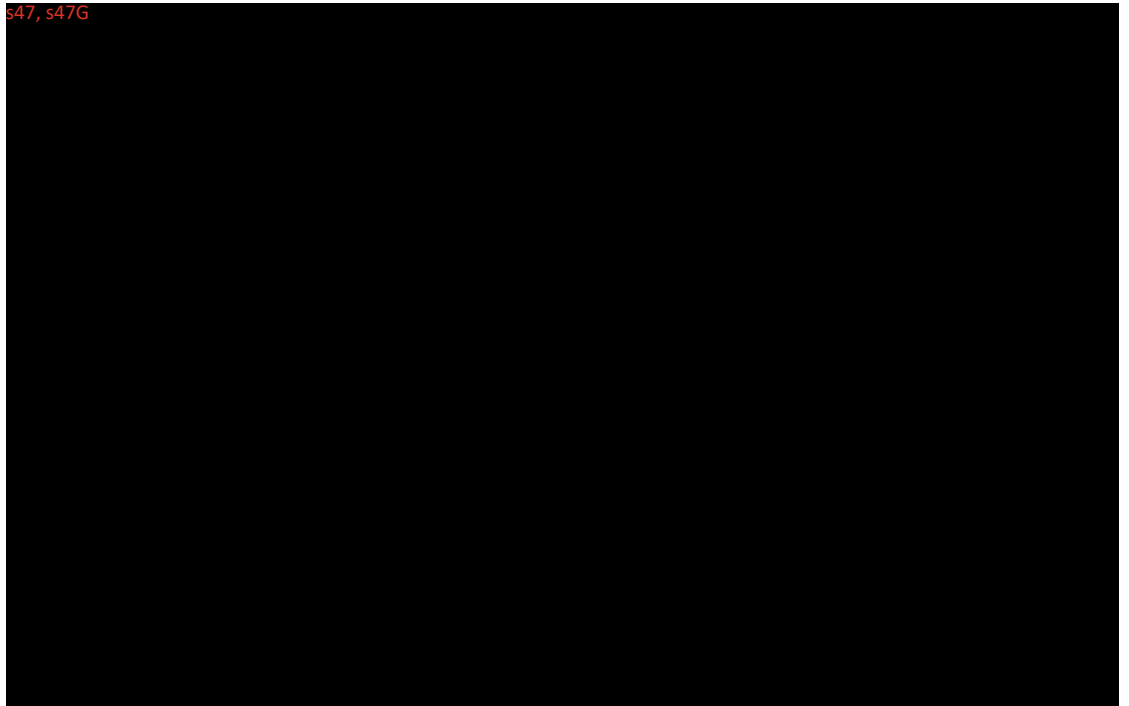
The number of cases recorded in Pfizer global safety database is extremely low (34 cases out of 110,714 total reports), compared to the volume of MPA used in the over 60 years since it was first approved and marketed (only in one year Q2 2022-Q1 2023, over 100 million units sold world-wide). In terms of age and treatment recommendation, no determination could be established of a more exposed population to growing a meningioma. In most of the reported cases, the treatment duration was over 2 years (long term use, with majority of cases reporting a latency between 5 and 20 years), confirming the reports from literature that prolonged use of medroxyprogesterone could have a contributory role to meningioma growth.

Additionally, there is increased scrutiny on progestins and progesterone in relation to meningiomas especially with long term use (as an example, latest precautionary recommendation from ANSM, that included DMPA, based on the EPI-PHARE report published in June 2023).

As a consequence, meningioma is to be considered an important potential risk, due to the invalidating potential of the tumor in certain cases and the need of warning the prescribers, suggesting discontinuation of treatment if a meningioma is diagnosed.

Proposal for core data sheet update: addition of a paragraph in section 4.4 Warning and precautions to the effect of: Meningiomas were reported following long term administration of progestins, including medroxyprogesterone acetate. Caution is advised when recommending medroxyprogesterone to patients with a personal or familial history of meningioma. The drug should be discontinued if a meningioma is diagnosed.

s47, s47G



Other actions

Do you intend to update your Australian Product Information document?

Yes

estimated date of submission

2024-01-15

Are you considering any other actions?

No

Supporting documents

Attachments

You will receive a copy of your submission to the contact email address provided.

When you receive this email, **please reply and attach any relevant supporting documents**, for example:

- sponsor assessment
- comparable overseas regulator assessment report
- any other relevant assessments

[Copy to Clipboard](#)

Product Name

MEDROXYPROGESTERONE

Signal Description

Meningioma

Primary Source

Scientific Literature

Date Signal Validated

18-May-2023

Date Completed

26-Sep-2023

Safety Signal Analysis

Medical Literature

Search Methodology

A literature search (Embase, BIOSIS Previews, Ovid MEDLINE(R), Google Scholar) for Risk AND (medroxyprogesterone OR MPA OR DMPA) AND meningioma

Analysis

The most relevant among recent literature sources are summarised below: Dewata et al., conducted case-control study in Soetomo Hospital (Indonesia). All female patients with meningioma were confirmed by pathologic anatomy result; patients in the control group were confirmed with non-meningioma by head CT-scan. Out of 212 cases, 184 patients (87%) used hormonal contraceptive, 13 patients used non-hormonal contraceptive IUD (6%), 15 patients (7%) used no method. Progestin-only (P) were used in 151 cases (86%), while combined-hormonal-contraceptive (Estrogen+Progestin) were used by 25 patients (14%). Three-monthly-injection of DMPA was the most common hormonal contraceptive used in 155 patients (73.1%), in which 63 patients (34.7%) used DMPA with duration of ≥ 15 years, 54 patients (31.2%) used 10–<15 years, 37 patients (22.9%) used 5–<10 years, 11 patients used 1–<5 years (7.6%), and <1 year in 6 patients (3.5%). Conclusion: Hormonal contraceptive was significantly increasing the risk for meningioma (OR 2.19 (CI 95%; 1.32–3.62)), the risk for meningioma was the highest among 3 monthly-injection of DMPA acceptors (OR 3.13 (CI 95%; 2.03–4.85)), and the longer

duration of exposure to DMPA will increase the risk for meningioma, with the highest risk in duration of 10–<15 years (OR 2.33 (CI 95%; 1.31–4.15)) and ≥ 15 years (OR 4.45 (CI 95%; 2.35–8.35)). EANO guideline on the diagnosis and management of meningiomas is citing Supartoto A. et al case control study that examined the expression of Progesterone receptor (PR) and Neurofibromatosis-2 (NF2) and assessed their relationships to history of exogenous progesterone use and risk of meningioma. The study involved 115 females, 40 cases who were diagnosed with orbito-cranial meningioma and 75 controls of healthy subjects. The demographic characteristics, reproductive factors, and history of progesterone use were obtained in-depth face-to-face interviews. PR and NF2 mRNA were assessed by real-time quantitative polymerase chain reaction (RT-qPCR) on serum specimens. Of note, 55.2% (N=21) subjects out of the 40 diagnosed cases were treated with 3-monthly injections (N.B. Depo-MPA is the only progestogen given at 3 month). The study showed that the longer the exposure to exogenous progesterone injection, the lower the expression of PR and NF2 mRNA in the serum, and that lower expression of PR and NF2 mRNA was significantly and independently associated with higher risk of females to suffer from orbitocranial meningioma. More importantly, a significant interaction between expression of PR and NF2, in which females who had low both expression of PR and NF2 had significantly increased risk of meningioma when compared to those who had higher expression of PR and NF2. These findings suggest that long exposure to exogenous progesterone may increase the risk of developing meningioma through lowering the expression of PR and NF2. Abou-al-Shaar et al. published in February 2023 the results of a retrospective review of meningioma patients with a history of depo-medroxyprogesterone (DMPA) use treated at the University of Pittsburgh Medical center between 2014 and 2021. Clinical and radiographic data as well as duration of consistent DMPA use were reported. Histopathological and immunohistochemical examinations of resected meningiomas was performed. During the study period, 25 female patients with a mean age of 46 years were identified to harbour one or more intracranial meningiomas related to chronic DMPA use. There were 49 total meningiomas (range: 1–6 meningiomas per patient). The mean duration of DMPA use was 15.5 years (range: 6–26). Seventeen (68%) patients had at least one skull base meningioma located in the sphenocavernous-orbital, sphenocavernous, sphenoorbital, or orbital region. Histopathological examination of the 47 resected meningiomas identified that 36 (77%) were WHO grade I, 11 (23%) were WHO grade II and the mean Ki-67 proliferation index was 2.2% (range: 1–5%). Progesterone immunohistochemical staining was performed on all meningiomas and all tumors stained positively for it. Interestingly, 10 patients were instructed to stop DMPA that had either an untreated meningioma or a clear (≥ 1 cm) residual following surgical intervention. Among these 10 patients, 5 had clear evidence of tumour shrinkage, 2 were lost to follow-up, and 3 stopped DMPA within the past year not allowing for adequate assessment at this time of study. The authors concluded that there appears to be a clear progestin meningioma syndrome associated with chronic DMPA use. Patients with DMPA-associated meningiomas tend to be younger, middle-aged women with multiple meningiomas, of which one is commonly located at the skull base (sphenoid wing, orbit, and/or cavernous sinus). The meningiomas tend to be low grade meningiomas and often invade underlying bone and express progesterone receptor on immunohistochemical staining. Females that fit these criteria should be screened and counselled for progestin use. The agent should be stopped immediately, and the patient should be closely followed before other treatments are entertained. An interesting case was described by Hensiek A.E., et al. in an article published in 2009. This was a case of a 44-year-old male patient (s22) with regression of a probable cerebral metastasis of a hypernephroma after nephrectomy and hormone therapy (MPA). The patient subsequently developed a meningioma, 4 years after therapy with medroxyprogesterone acetate was initiated. A craniotomy with total excision of the olfactory groove mass was performed, which proved to be a meningothelial meningioma. No progesterone receptors could be detected in the tumour tissue (either in cytoplasm or nucleus) using a labelled streptavidin biotin method with microwave antigen retrieval. The patient made a good recovery with no residual neurological symptoms. The authors concluded that even though it is not possible to prove a correlation between the hormone therapy and the tumour growth, they believe that there is a likely link, especially in view of the absent progesterone receptors in this patient's meningioma. It has been demonstrated and is relevant to the case that binding of medroxyprogesterone acetate leads to a decrease in progesterone receptor concentration in meningiomas. Furthermore, the tumour could not be detected on routine scanning 1 year before diagnosis, which suggests a rather fast growing meningioma. Roland N. et Al., published in June 2023 a case-control study conducted using data from the National Health Data System (NSDS) in France. They analysed all cases of women who underwent intracranial meningioma surgery between 2009 and 2018. For each case, the index date was the date of entry of the hospital stay related to the intervention. In addition, women who had an early pregnancy within 2 years before the index date were excluded from the study. Each case was

randomly associated with 5 control women who had not undergone meningioma surgery up to index date, matching on year of birth and department of residence, according to the risk set sampling approach. For orally, percutaneously, intravaginal or intramuscular progestogens, exposure was defined as at least one delivery in the rolling year prior to the index date. For IUDs, dispensing was sought within 3 years prior to the index date for levonorgestrel 13.5 mg dosing, and within 5 years prior to the 52 mg dosage, according to the respective recommendations in force for device renewal and/or withdrawal. A total of 18,061 women undergoing meningioma surgery were included in the study, matched with 90,305 control women (15,162 cases and 75,810 controls for 52 mg IUDs over a limited period 2011-2018, and 4,048 cases and 20,240 controls for 13.5 mg IUDs over a restricted period 2017-2018). Of the 18,061 cases, 329 (1.8%) used oral or intravaginal progesterone before index date, 90 (0.5%) percutaneous progesterone, 42 (0.2%) medrogestone 5 mg, 156 (0.9%) dydrogesterone, 9 (0.05%) medroxyprogesterone acetate 150 mg, 83 (0.5%) promegestone 0.5 mg, 566 (3.7%) the levonorgestrel 52 mg IUD, and 10 (0.2%) the 13.5 mg IUD. An excess risk of meningioma was observed for exposure to medrogestone (OR 3.49 [95% confidence interval 2.38-5.10]), medroxyprogesterone acetate (OR 5.55 [2.27-13.56]), and promegestone (OR 2.39 [1.85-3.09]). For the three progestogens with an over-risk of meningioma (medrogestone, medroxyprogesterone acetate and promegestone), the excess risk associated with prolonged use (≥ 1 year) was higher than that measured for all durations of exposure combined (short and prolonged) (respectively: OR 4.08 [2.72-6.10]; 5.62 [2.19-14.42] and 2.74 [2.04-3.67]). The FAP of meningiomas exposed to medrogestone, promegestone and medroxyprogesterone acetate was 0.2%, 0.3% and 0.04% (of all cases), respectively, corresponding to 30, 48 and 7 cases of meningiomas operated during the period 2009-2018. Conclusions: This large epidemiological study once again confirms an effect of progestogens on the risk of operated intracranial meningioma. Prolonged use of promegestone 0.5 mg (OR 2.7), medrogestone 5 mg (OR 4.1), and medroxyprogesterone acetate 150 mg (OR 5.6) are found to be associated with meningioma risk. Note: based on the above report, ANSM (the French Health Authority) published preliminary recommendations for local guidelines for patients receiving progestines, including Depo-Provera - Preliminary recommendations defined in March and maintained in July 2023: In the event of a history of meningioma or existing meningioma, progestogen treatment should not be used, except in exceptional cases to be evaluated in a multidisciplinary consultation meeting (gynecologist and/or endocrinologist and neurosurgeon) on the basis of the individual benefit/risk ratio for the person and the presence or not of therapeutic alternatives; Before any new prescription or switch between progestins (in particular switching after treatment with cyproterone, nomegestrol or chlormadinone), check all the progestins already used and their duration of use during the patient's lifetime; Prescribe at the minimum effective dose with the shortest possible duration of use; Regularly reassess the treatment (annually), especially around menopause, the risk of meningioma increasing sharply with age; Perform a brain MRI in case of neurological clinical signs suggestive of a meningioma (headaches, visual, language, memory and hearing disorders, nausea, dizziness, convulsions, loss of smell, weakness or paralysis).

Pfizer Post-Marketing Safety Data

Search Methodology

A global safety data base search has been conducted for medicinal products containing medroxyprogesterone and all PTs that contain the word "meningioma", cumulatively through 10 May 2023.

Analysis

A global safety data base search has been conducted for medicinal products containing medroxyprogesterone and all PTs that contain the word "meningioma", cumulatively through 10 May 2023. Out of 110,714 cases reported in total for medroxyprogesterone, 34 cases (0.03%) reported a diagnosis of meningioma. All 34 cases were reviewed in detail. Of the 34 cases, there were 33 females and 1 male. When reported ($n=27$), age range was 28 – 60 years, with a mean age of 48.8. The reports originated from United Kingdom (12), United States (11), Germany and Netherlands (3 cases each), Austria, Belgium, Italy, Japan and New Zealand (1 case each). Out of the 34 cases, 30 were spontaneously reported, 3 originated from literature and 1 case was from a Pfizer clinical trial (a woman developing meningioma after 7 years of MPA treatment). In 2 cases, a pre-existing family history of meningioma was present. In majority of cases, the treatment with MPA was ongoing for a long time

(5-20 years) when meningioma was diagnosed. Indication for MPA treatment was contraception (15 cases), hormone replacement therapy (HRT) (5), lymphangiomyomatosis (LAM) (4), endometriosis (2), renal cell carcinoma, uterine cancer, and dysmenorrhoea (1 case each). Indication was not reported in 5 cases. Dosage was not reported in 25 cases, while in 2 cases multiple products are listed with various dosages; high dose of MPA was described in the 4 cases of LAM treatment (oral doses of 200 mg and 400 mg and monthly injection of 500 mg and “high dose”); in the remaining 3 cases the patients received 150mg inj. / 3 month (2 cases) and a dose described as 10 mg in the last case. There were 33 cases assessed as serious, while 1 case was assessed as not serious ^{s22} reported in 1993, from spontaneous source, does not contain sufficient information for proper evaluation). Case outcome was reported as not resolved in 12 cases, resolved in 3 cases, resolved with sequelae in 5 cases, resolving in 5 cases and unknown in 10 cases. In 5 spontaneously reported cases, there were very limited details provided, that would not allow for an assessment. In 3 cases, withdrawal of MPA lead to reduction or complete resolution of symptoms.

Analysis and Data Assessment

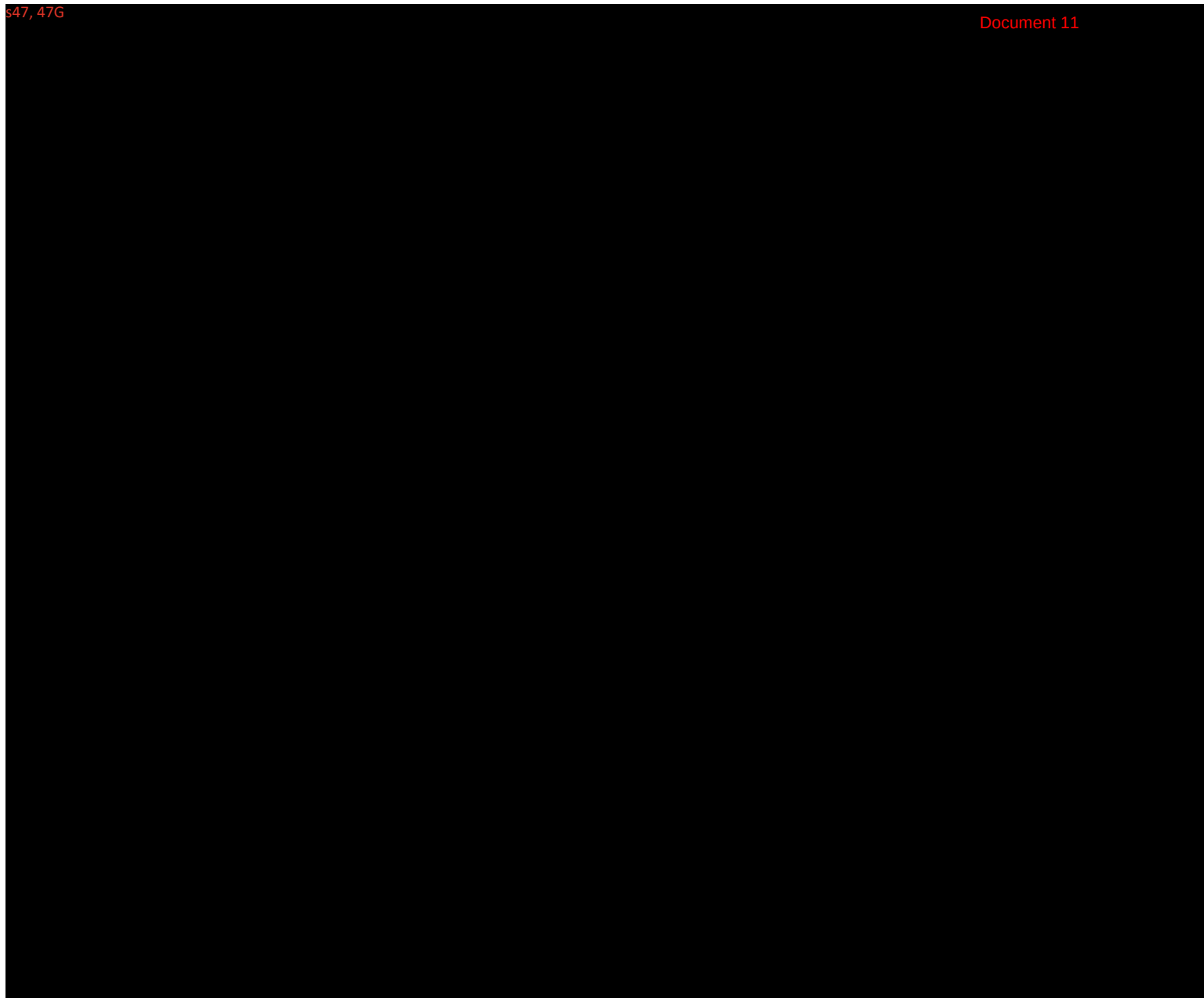
Even though there are multiple literature sources discussing the influence of medroxyprogesterone in the development and growth of meningiomas, a definite sole association cannot be established, due to multiple other factors involved in the etiology of meningiomas (genetic, environmental, traumatic, etc). In the general population, according to the Central Brain Tumor Registry of the United States Statistical Report, of tumors diagnosed in the U.S. alone in 2012-2016, meningiomas were the most frequently reported overall histology (37.6%) of all primary central nervous system tumors with 33,560 cases projected in 2019. The average annual age-adjusted incidence rate was also highest for meningiomas (8.6 per 100,000 people) of all primary brain and spinal cord tumors.

The number of cases recorded in Pfizer global safety database is extremely low (34 cases out of 110,714 total reports), compared to the volume of MPA used in the over 60 years since it was first approved and marketed (only in one year Q2 2022-Q1 2023, over 100 million units sold world-wide). In terms of age and treatment recommendation, no determination could be established of a more exposed population to growing a meningioma. In most of the reported cases, the treatment duration was over 2 years (long term use, with majority of cases reporting a latency between 5 and 20 years), confirming the reports from literature that prolonged use of medroxyprogesterone could have a contributory role to meningioma growth.

Additionally, there is increased scrutiny on progestins and progesterone in relation to meningiomas especially with long term use (as an example, latest precautionary recommendation from ANSM, that included DMPA, based on the EPI-PHARE report published in June 2023).

As a consequence, meningioma is to be considered an important potential risk, due to the invalidating potential of the tumor in certain cases and the need of warning the prescribers, suggesting discontinuation of treatment if a meningioma is diagnosed.

Proposal for core data sheet update: addition of a paragraph in section 4.4 Warning and precautions to the effect of: *Meningiomas were reported following long term administration of progestins, including medroxyprogesterone acetate. Caution is advised when recommending medroxyprogesterone to patients with a personal or familial history of meningioma. The drug should be discontinued if a meningioma is diagnosed.*



Potential Risk
Important: Yes

From: tga.no-reply@govcms.gov.au
To: [Signal Investigation Coordinator](#)
Subject: Medicine safety notification: Pfizer Australia Pty Ltd : Medroxyprogesterone (Depo-Provera, Provera, Depo-Ralovera, Ralovera and Sayana) and Meningioma
Date: Thursday, 26 October 2023 9:51:35 AM

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Submitted on Thu, 2023-10-26 09:37

Submitted by: Anonymous

Submitted values are:

Reporter details

Reporting sponsor

Pfizer Australia Pty Ltd

Reporters name

s22

Contact email address

s22

@pfizer.com

Issue details

Safety issue

Medroxyprogesterone (Depo-Provera, Provera, Depo-Ralovera, Ralovera and Sayana) and Meningioma

Type of safety issue

OSI - Other safety issue

Date of local awareness by the sponsor (Day 0)

2023-09-26

Type of notification

Initial

Product details

Is your company the product innovator?

Yes

Product details

- **Product name:** DEPO-PROVERA medroxyprogesterone acetate 150 mg/mL aqueous suspension injection vial
ARTG no.: 12300
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA medroxyprogesterone acetate 100mg tablet
ARTG no.: 12331
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA medroxyprogesterone acetate 200mg tablet
ARTG no.: 12333
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA medroxyprogesterone acetate 250mg tablet
ARTG no.: 12334
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA medroxyprogesterone acetate 500mg tablet
ARTG no.: 12336
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA Medroxyprogesterone acetate 2.5mg tablet
ARTG no.: 42932
Active ingredient(s): Medroxyprogesterone acetate
Australian sponsor: Pfizer Australia
Marketed in Australia: Yes
- **Product name:** PROVERA Medroxyprogesterone acetate 5mg tablet
ARTG no.: 42933

Issue source

Safety issue source

Comparable overseas regulator

Safety issue summary

PRAC requested a review of the signal of Meningioma on 18-May-2023. Review of the signal concluded on 26-Sep-2023 which confirmed the signal as an important potential risk. Notification of the signal from above country Pfizer colleagues was received 26-Sep-2023.

A literature search (Embase, BIOSIS Previews, Ovid MEDLINE(R), Google Scholar) for Risk AND (medroxyprogesterone OR MPA OR DMPA) AND meningioma.

A global safety data base search has been conducted for medicinal products containing medroxyprogesterone and all PTs that contain the word "meningioma", cumulatively through 10 May 2023.

Even though there are multiple literature sources discussing the influence of medroxyprogesterone in the development and growth of meningiomas, a definite sole association cannot be established, due to multiple other factors involved in the etiology of meningiomas (genetic, environmental, traumatic, etc). In the general population, according to the Central Brain Tumor Registry of the United States Statistical Report, of tumors diagnosed in the U.S. alone in 2012-2016, meningiomas were the most frequently reported overall histology (37.6%) of all primary central nervous system tumors with 33,560 cases projected in 2019. The average annual age-adjusted incidence rate was also highest for meningiomas (8.6 per 100,000 people) of all primary brain and spinal cord tumors.

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Other actions

Do you intend to update your Australian Product Information document?

Yes

estimated date of submission

2024-01-15

Are you considering any other actions?

No

Supporting documents

Attachments

You will receive a copy of your submission to the contact email address provided.

When you receive this email, **please reply and attach any relevant supporting documents**, for example:

- sponsor assessment
- comparable overseas regulator assessment report
- any other relevant assessments