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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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, s22 [redacted] 401610, s22 [redacted]

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, s22 [redacted] 401610, s22 [redacted]

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

[redacted]

Document generated **1/02/2024 22:53 PM**

Document 2

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
s22	[redacted]

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.

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), s 22 [redacted]

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	s 22 [redacted]

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,

s22 [redacted]

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Lifecycle Management Tracking Table

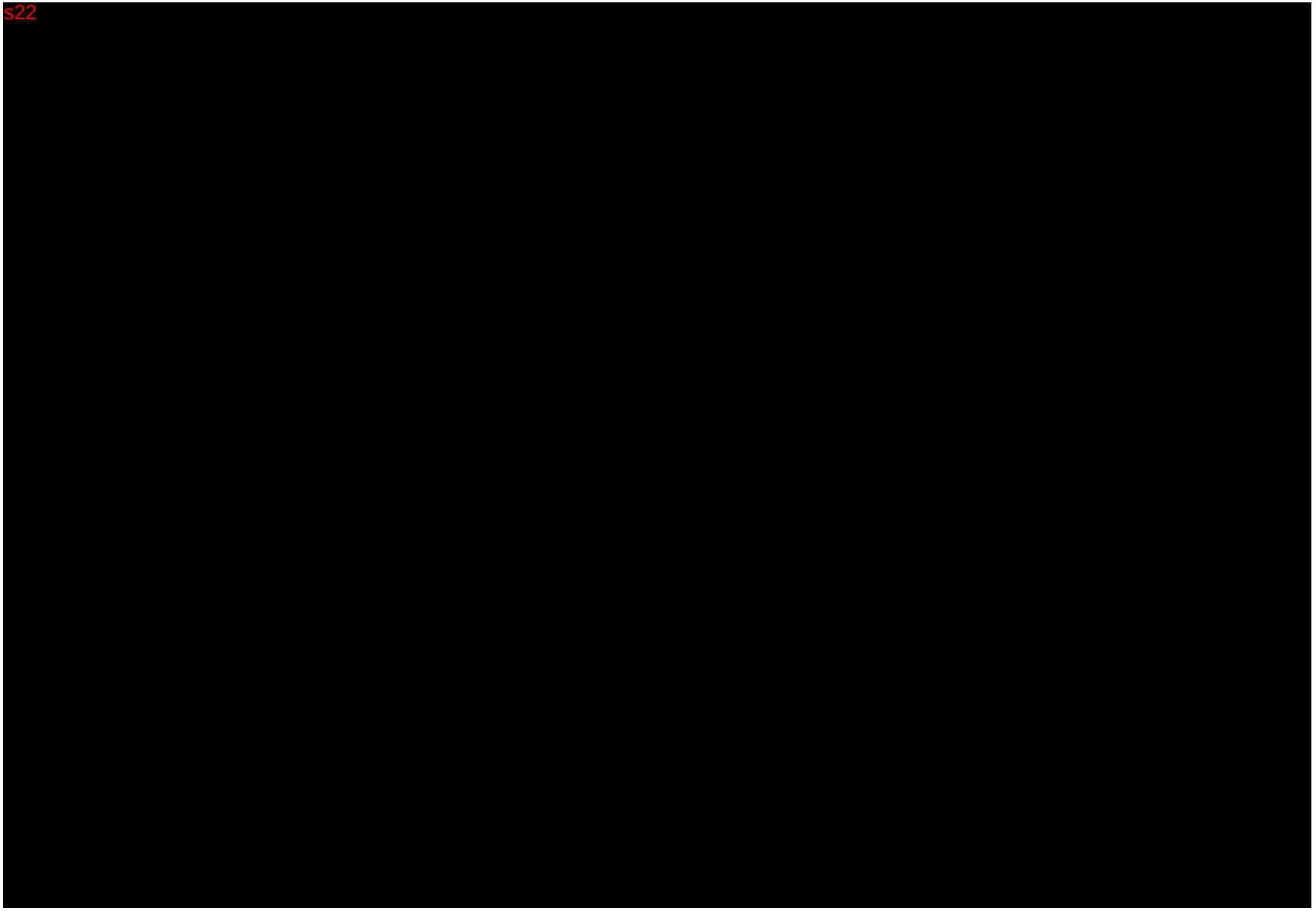
DEPO-PROVERA® (medroxyprogesterone acetate) 150 mg/mL injection, vial, AUST R 12300.
DEPO-PROVERA® (medroxyprogesterone acetate) 150 mg/mL injection, pre-filled syringe, AUST R 401610

s22 [redacted]

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

s22 [redacted]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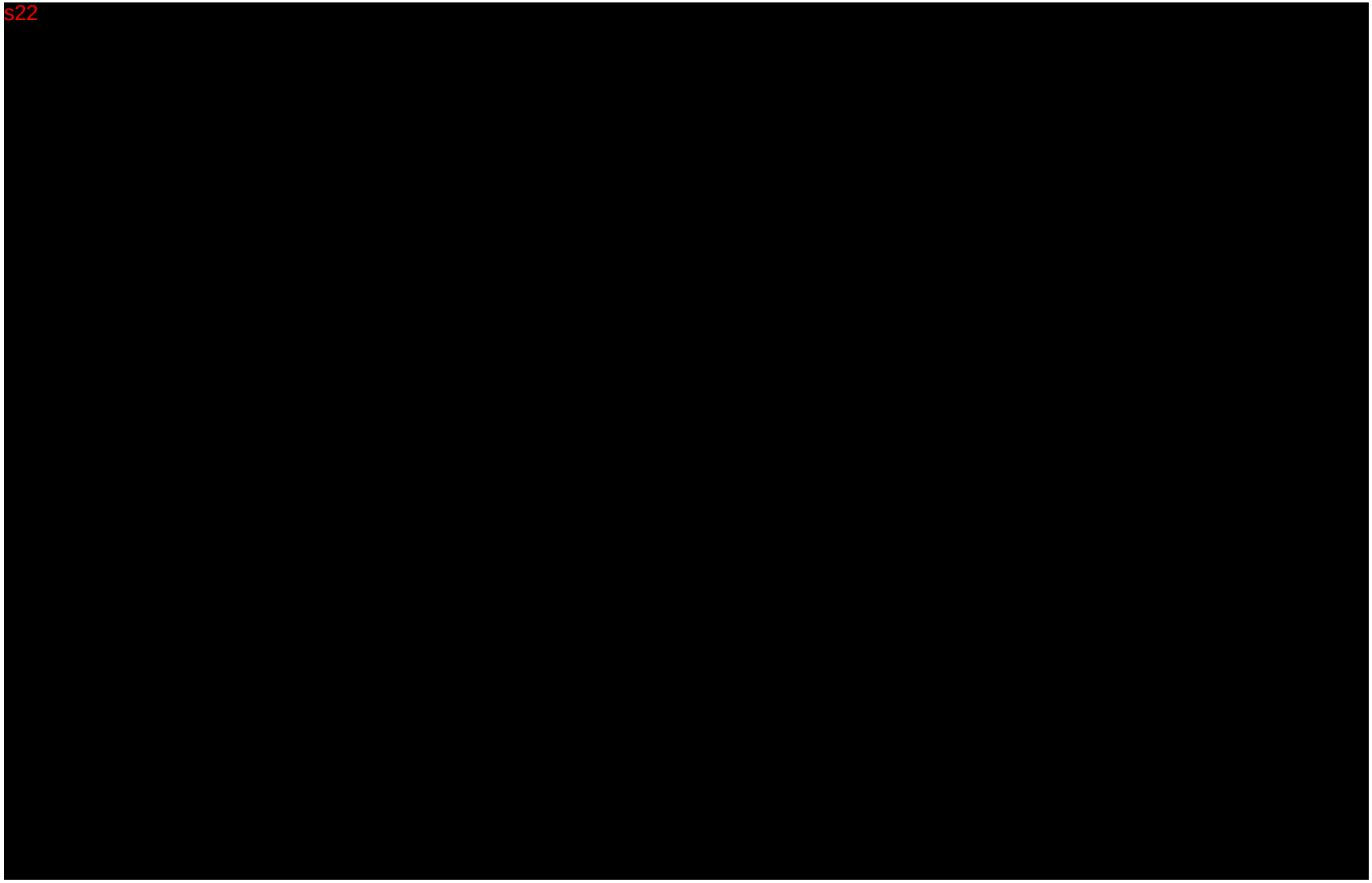
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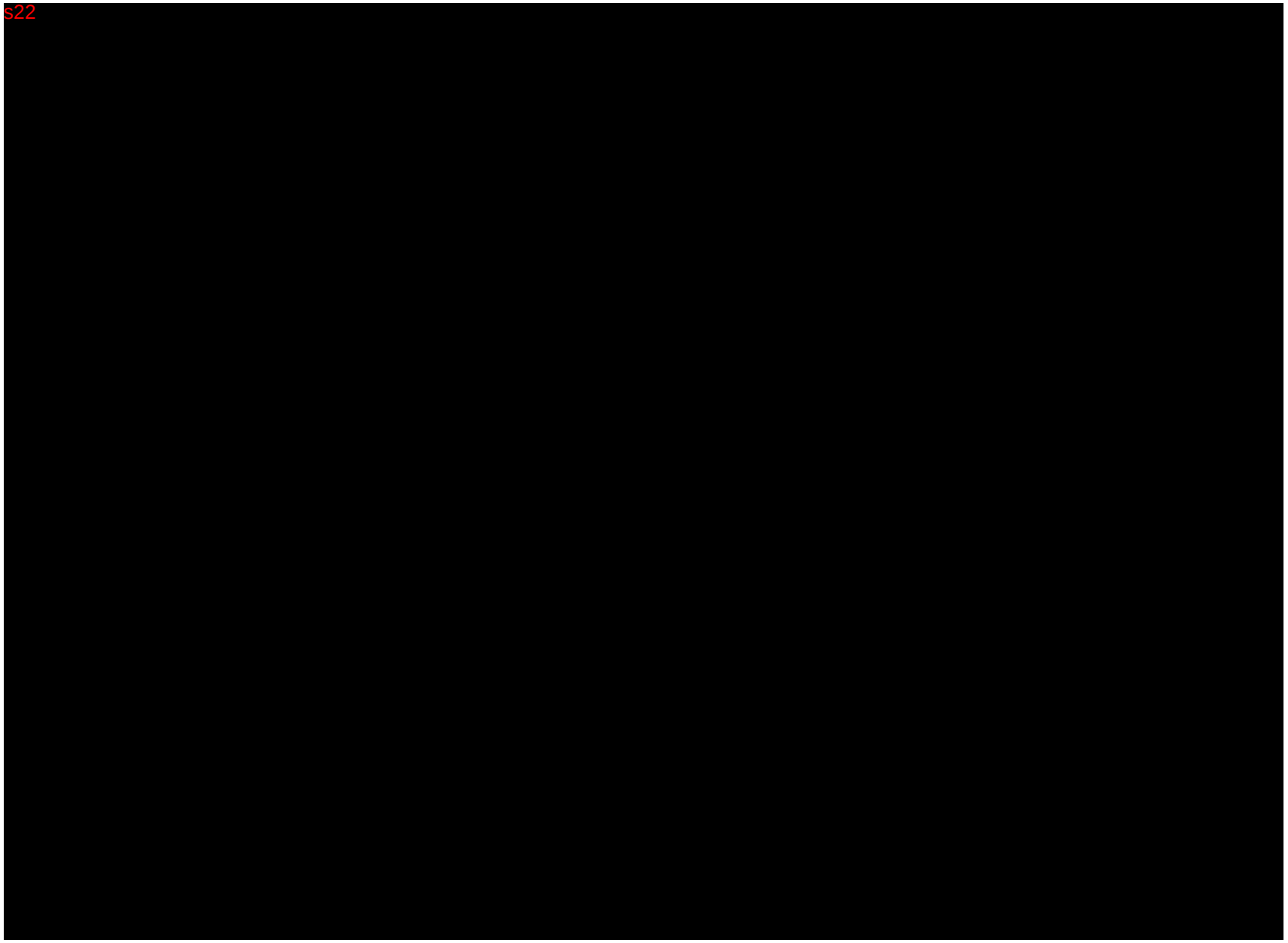
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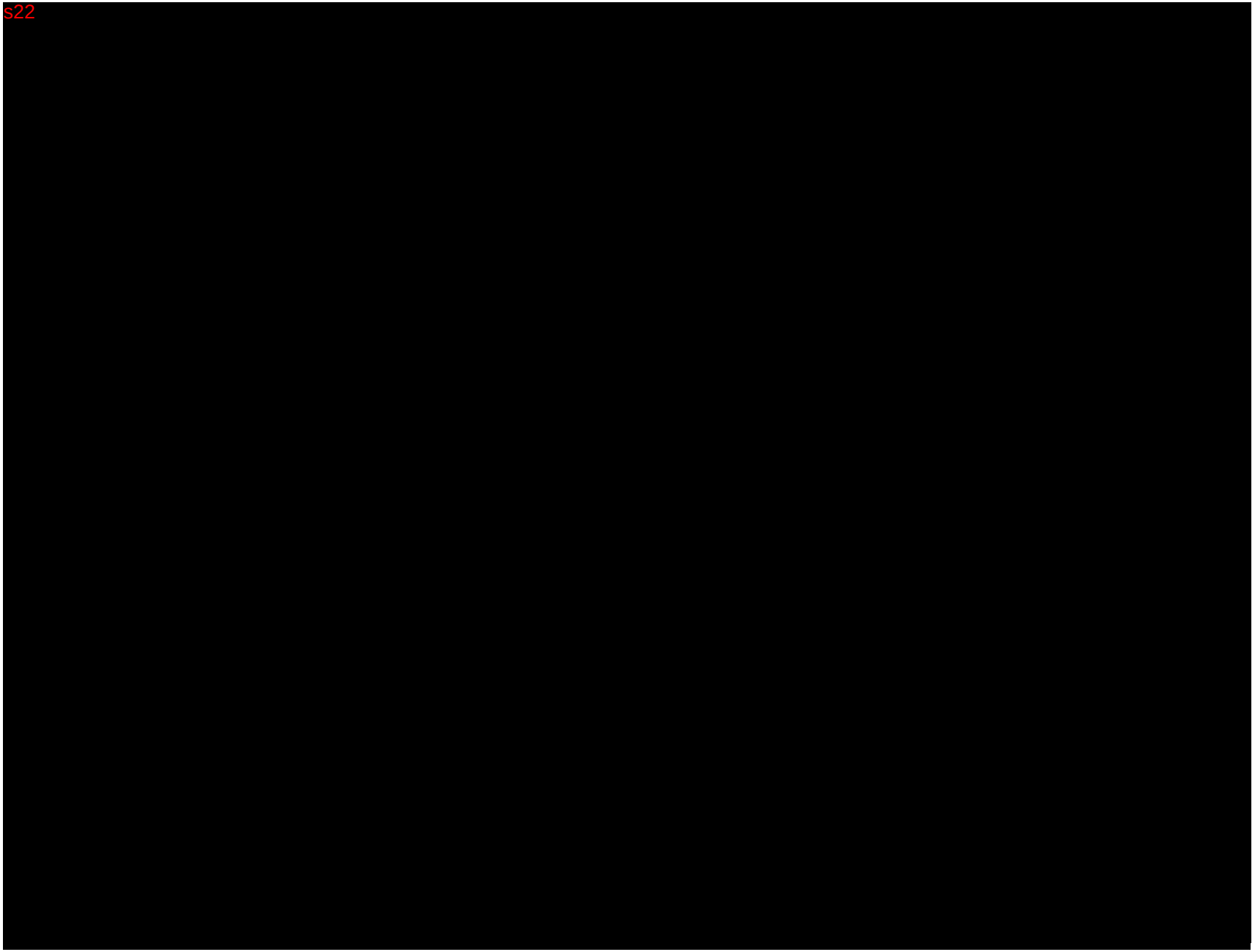
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AUSTRALIAN PRODUCT INFORMATION – DEPO-PROVERA® (MEDROXYPROGESTERONE ACETATE)

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 ~~m~~Month 12, amenorrhoea was reported by 57% of women, and by ~~m~~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 pre-menopausal 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.
- Hepatobillary 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

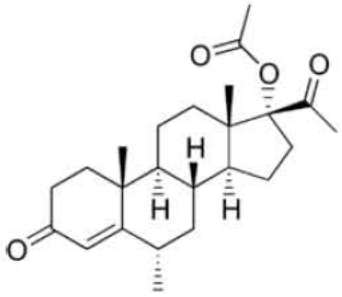
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

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 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate, the molecular formula is $C_{24}H_{34}O_4$ 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 [x2]: 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.

9. DATE OF FIRST APPROVAL

2 August 1991~~.~~

10. DATE OF REVISION

~~03 May 2023~~DD 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-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 pre-menopausal 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.
- Hepatobillary 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.

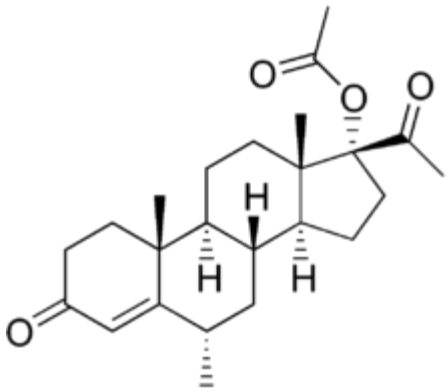
6.7 Physicochemical properties

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 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate, the molecular formula is $C_{24}H_{34}O_4$ 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

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Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

The s22
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
- s22
- 401610 - DEPO-PROVERA medroxyprogesterone acetate 150 mg/1 mL suspension for injection pre-filled syringe
- s22

(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/s22 medroxyprogesterone acetate injection (changes highlighted)
      s 22
   b. DEPO-PROVERA/s22 medroxyprogesterone acetate injection (clean)
      s 22

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 Government

Department of Health and Aged Care

Therapeutic Goods Administration

The s22
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

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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.

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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

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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.

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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 ~~m~~Month 12, amenorrhoea was reported by 57% of women, and by ~~m~~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 pre-menopausal 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.
- Hepatobillary 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

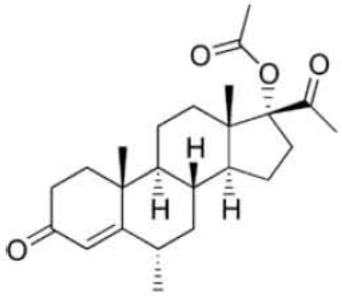
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

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 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate, the molecular formula is $C_{24}H_{34}O_4$ 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 [redacted]: 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.

9. DATE OF FIRST APPROVAL

2 August 1991~~.~~

10. DATE OF REVISION

~~03 May 2023~~DD 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-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 pre-menopausal 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.
- Hepatobillary 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.

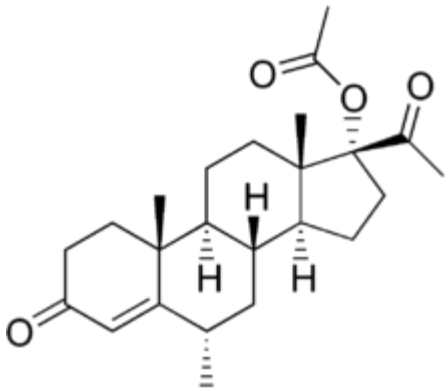
6.7 Physicochemical properties

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 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate, the molecular formula is $C_{24}H_{34}O_4$ 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

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From: s22
To: s22 @pfizer.com
Cc: RegulatoryAffairs.ANZ@pfizer.com
Subject: 9D(2) SRR & 9D(3) MEC - [Approval letter] - PM-2024-00437-1-4 - DEPO-PROVERA s22 s22 medroxyprogesterone acetate injection/s22 - 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 s22 s22 - medroxyprogesterone acetate injection s22 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

LICENCE_IDENTIFIER	LICENCE_NAME	SPONSOR
AUST R 167889	SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe	Pfizer Australia Pty Ltd
AUST R 59299	PREMIA 5 CONTINUOUS tablet blister pack	Pfizer Australia Pty Ltd
AUST R 59300	PREMIA 2.5 CONTINUOUS tablet blister pack	Pfizer Australia Pty Ltd
AUST R 79252	MEDROXYPROGESTERONE SANDOZ medroxyprogesterone acetate 10mg tablet blister pack	Sandoz Pty Ltd
AUST R 80614	PREMIA LOW 0.3/1.5 CONTINUOUS tablet blister pack	Pfizer Australia Pty Ltd
AUST R 80615	PREMIA LOW 0.45/1.5 CONTINUOUS tablet blister pack	Pfizer Australia Pty Ltd
AUST R 12279	DEPO-PROVERA C150 medroxyprogesterone acetate 150mg/mL Aqueous Suspension injection syringe	Pfizer Australia Pty Ltd
AUST L 42472	PROVETTE 1.25 tablet blister pack	Pfizer Australia Pty Ltd
AUST L 42475	PROVETTE 0.625 tablet blister pack	Pfizer Australia Pty Ltd
AUST R 12301	DEPO-PROVERA medroxyprogesterone acetate 50mg/1mL injection vial	Pfizer Australia Pty Ltd
AUST R 44463	DEPO-RALOVERA medroxyprogesterone acetate 50mg/1mL injection vial	Pfizer Australia Pty Ltd
AUST R 41629	RALOVERA medroxyprogesterone acetate 100mg tablets blister pack	Pfizer Australia Pty Ltd
AUST R 41630	RALOVERA medroxyprogesterone acetate 200mg tablet blister pack	Pfizer Australia Pty Ltd
AUST R 41631	RALOVERA medroxyprogesterone acetate 250mg tablet blister pack	Pfizer Australia Pty Ltd
AUST R 41632	RALOVERA medroxyprogesterone acetate 500mg tablet blister pack	Pfizer Australia Pty Ltd
AUST R 59298	PREMIA 5 tablet blister pack (composite pack)	Wyeth Australia Pty Limited
AUST R 77429	PREMIA 10 tablet composite pack	Wyeth Australia Pty Limited
AUST R 79258	MEDROXYHEXAL medroxyprogesterone acetate 10mg tablet bottle	Sandoz Pty Ltd
AUST R 12335	PROVERA medroxyprogesterone acetate 400mg tablet bottle	Pfizer Australia Pty Ltd
AUST R 41633	RALOVERA medroxyprogesterone acetate 400mg tablet bottle	Pfizer Australia Pty Ltd
AUST R 47040	DEPO-RALOVERA medroxyprogesterone acetate 150mg/1mL injection syringe	Pfizer Australia Pty Ltd
AUST R 12329	PROVERA ORAL SUSPENSION medroxyprogesterone acetate 500mg/5mL bottle	Pfizer Australia Pty Ltd
AUST R 15412	FARLUTAL medroxyprogesterone acetate 500mg/2.5mL injection vial	Pfizer Australia Pty Ltd
AUST R 15413	FARLUTAL 100 (Medroxyprogesterone Acetate) 100mg Tablets	Pfizer Australia Pty Ltd

AUST R 15414	FARLUTAL 200 (Medroxyprogesterone Acetate) 200mg Tablets	Pfizer Australia Pty Ltd
AUST R 15415	FARLUTAL 500 (Medroxyprogesterone Acetate) 500mg Tablets	Pfizer Australia Pty Ltd
AUST R 41634	RALOVERA medroxyprogesterone acetate 500mg/5mL oral suspension bottle	Pfizer Australia Pty Ltd
AUST R 75478	MENOVERA-14 tablet blister pack	Pfizer Australia Pty Ltd
AUST R 75479	PROGENA-14 tablet blister pack	Pfizer Australia Pty Ltd
AUST R 75480	MENOVERA-28 tablet blister pack	Pfizer Australia Pty Ltd
AUST R 75481	PROGENA-28 tablet blister pack	Pfizer Australia Pty Ltd
AUST R 46095	DIVINA tablets blister pack	
AUST L 41364	MENOPREM Premarin 0.625 mg and Provera 10 mg tablet blister pack	Wyeth Australia Pty Limited
AUST R 67427	MENOPREM premarin 0.625mg tablet & cycrin 10mg composite pack blister pack	Wyeth Australia Pty Limited
AUST R 67428	CYCRIN 10mg medroxyprogesterone acetate 10mg tablet blister pack	Wyeth Australia Pty Limited
AUST R 67429	CYCRIN 5mg medroxyprogesterone acetate 5mg tablet blister pack	Wyeth Australia Pty Limited
AUST R 67430	CYCRIN 2.5mg medroxyprogesterone acetate 2.5mg tablet blister pack	Wyeth Australia Pty Limited
AUST R 67431	MENOPREM CONTINUOUS premarin 0.625mg tablet and cycrin 5mg tablet composite pack tablet pack	Wyeth Australia Pty Limited
AUST C 44556	ESTRAPAK 50 OESTRADIOL 4mg Transdermal Drug Delivery System with Medroxyprogesterone Acetate 10mg tablet blister pack	Novartis Pharmaceuticals Australia Pty Ltd
AUST C 46415	ERA medroxyprogesterone acetate 2.5mg tablet blister pack	Wyeth Australia Pty Limited
AUST C 46416	ERA medroxyprogesterone acetate 5mg tablet blister pack	Wyeth Australia Pty Limited
AUST C 46417	ERA medroxyprogesterone acetate 10mg tablet blister pack	Wyeth Australia Pty Limited
AUST C 50286	ERA medroxyprogesterone acetate 2.5mg tablet bottle	Wyeth Australia Pty Limited
AUST C 50287	ERA medroxyprogesterone acetate 5mg tablet bottle	Wyeth Australia Pty Limited
AUST C 50288	ERA medroxyprogesterone acetate 10mg tablet bottle	Wyeth Australia Pty Limited
AUST C 12330	PROVERA medroxyprogesterone acetate 10mg tablet bottle	Pharmacia Australia Pty Limited
AUST C 12332	PROVERA medroxyprogesterone acetate 2.5mg tablet bottle	Pharmacia Australia Pty Limited
AUST C 12337	PROVERA medroxyprogesterone acetate 10mg tablet blister pack	Pharmacia Australia Pty Limited
AUST C 12338	PROVERA medroxyprogesterone acetate 5mg tablet blister pack (OF)	Pharmacia Australia Pty Limited
AUST C 46418	PROVELLE-14 Premarin 0.625mg and PROVERA 10mg tablet blister pack (OF)	Pharmacia Australia Pty Limited

AUST C 43577	MENOPREM Premarin 0.625 mg and PROVERA 10mg tablet, blister pack (OF)	Wyeth Australia Pty Limited