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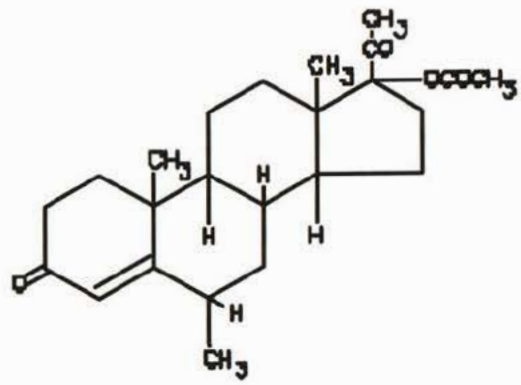
DEPO-PROVERA®

Injection Suspension

(medroxyprogesterone acetate)

DESCRIPTION

Medroxyprogesterone acetate is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 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. Medroxyprogesterone acetate is 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate and its structural formula is as follows:



DEPO-PROVERA injection suspension is supplied in the following strengths and packages:

50 mg/1 mL vial - each mL contains 50 mg medroxyprogesterone acetate, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and water for injections.

150 mg/1 mL vial - each mL contains 150 mg medroxyprogesterone acetate, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and water for injections.

PHARMACOLOGY

Animal

Medroxyprogesterone acetate 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. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

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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 oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In five 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).[1,2] 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.

Pharmacokinetics

Parenteral medroxyprogesterone acetate 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 medroxyprogesterone acetate (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 intramuscular medroxyprogesterone acetate.

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

CLINICAL TRIALS

BMD Changes in Adult Women[3]

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 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 WARNINGS.

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BMD Changes in Adolescent Females (12-18 years) [5, 6]

Preliminary results from an ongoing, open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See WARNINGS.

INDICATIONS

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

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

3. **Contraception (ovulation suppression):** For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-PROVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see WARNINGS).[4]

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-PROVERA 150 mg/1 mL, should be used for contraception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions

2. Markedly impaired liver function

3. Undiagnosed vaginal bleeding

4. Undiagnosed urinary tract bleeding

5. Undiagnosed breast pathology

6. Missed abortion

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7. Known sensitivity to medroxyprogesterone acetate or any of the excipients - see DESCRIPTION

8. Known or suspected pregnancy - See PRECAUTIONS, Use in Pregnancy

9. Severe uncontrolled hypertension

10. Known or suspected malignancy of the breast (excluding use in oncology indications)

WARNINGS

1. **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.

2. **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.

3. **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.[8]

   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.

4. **Bone Mineral Changes:**

   Contraception and Endometriosis: Use of DEPO-PROVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen 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 both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian oestrogen production increases.[4] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[6]

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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.[4] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[4] Since loss of bone mineral density (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.[4]

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 CLINICAL TRIALS.

Oncology: There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, 2 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 CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-PROVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[23]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[23]

It is recommended that all patients have adequate calcium and Vitamin D intake.[7]

5. **Cancer Risks:** Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[9] and no increased overall risk of ovarian,[10] liver,[11] or cervical[12] cancer. There was a prolonged effect of reducing the risk of endometrial[13] 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 relative risk of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89)[9] 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 relative risk increases in women aged between 25 and 34 years of age (RR: 2 (95% CI 1.0-3.8) and rises to 4.6

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(95% CI 1.4-15.1) in women aged less than 25 years with more than 2 years exposure to DEPO-PROVERA.[14] The risk of breast cancer[9] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[15] 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 Relative Risk 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 relative risk 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 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

6. **Accidental Pregnancies:** Infants from accidental pregnancies that occur 1-2 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.[16,17]

   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.[18]

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

8. **Sexually Transmitted Diseases:** DEPO-PROVERA 150 mg/1 mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

10. 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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

11. Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.

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12. The following laboratory tests may be affected by the use of DEPO-PROVERA:
    a. Gonadotrophin levels
    b. Plasma progesterone levels
    c. Urinary pregnanediol levels
    d. Plasma testosterone levels (in the male)
    e. Plasma oestrogen levels (in the female)
    f. Plasma cortisol levels
    g. Glucose Tolerance Test
    h. Metyrapone Test - the use of medroxyprogesterone acetate 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.
    i. Sex-hormone-binding-globulin concentrations are decreased.
    j. Coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

13. **Drug Interactions:** Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of medroxyprogesterone acetate.[19] DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

PRECAUTIONS

1. **Physical Examination:** The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

2. **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.

3. **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.

4. **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.

5. **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.

6. **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 kgs (136 lbs) women who completed 1 year of therapy with DEPO-PROVERA gained an

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average of 2.45 kgs (5.4 lbs). Women who completed 2 years of therapy gained an average of 3.68 kgs (8.1 lbs). Women who completed 4 years gained an average of 6.3 kgs (13.8 lbs). Women who completed 6 years gained an average of 7.5 kgs (16.5 lbs). Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

7. **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.

8. **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.

9. **Hepatic Insufficiency:** 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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

10. **Patient Age:** The age of the patient constitutes no absolute limiting factor, although treatment with progestins may mask the onset of the climacteric.

11. **Pathology Tests:** The pathologist should be advised of progestin therapy when relevant specimens are submitted.

12. **IM Administration:** Gluteal infiltration and abscess formation may occur with intramuscular administration. The IM suspension is not formulated for subcutaneous injection. See DOSAGE AND ADMINISTRATION.

13. 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.

14. Medroxyprogesterone acetate used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in pregnancy: Category D

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

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

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

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 five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION)

(See also WARNINGS, item 6)

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.

Use in children

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[5,6] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for postmenarcheal adolescent and adult females.[4]

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ADVERSE REACTIONS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

1. Anaphylaxis, anaphylactoid-like reactions, angioedema

2. Cardiovascular - thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure

3. Central Nervous System - nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders

4. 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

5. Skin and mucous membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating

6. Gastrointestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function

7. Breast – mastodynia, tenderness, galactorrhoea

8. Cervix - changes in the position of the transformation zone and in secretions

9. Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia

10. Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts

11. Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria

12. Genitourinary – prolonged anovulation

In a clinical trial conducted using DEPO-PROVERA for contraception over 3900 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 &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- Nervousness
- Headache

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- 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

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

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[20,21,22].

DOSAGE AND ADMINISTRATION

Indications	Dosage
Inoperable, recurrent, metastatic, endometrial & renal carcinoma	Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 weeks for maintenance.
Breast Carcinoma	IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.

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Endometriosis	50 mg weekly or 100 mg every two weeks by intramuscular injection for at least six 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.

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-PROVERA 150 mg/1 mL, should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years[4]. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications[23].

Gluteal infiltration and abscess formation may occur with intramuscular 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 intra-muscular injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental oestrogens 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 oestrogens in the equivalent of 0.05 to 0.1 mg ethinyl estradiol 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.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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.

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Contact the Poisons Information Centre for advice on the management of an overdose.

HOW SUPPLIED

DEPO-PROVERA (medroxyprogesterone acetate) injection suspension is supplied as:

50 mg/1 mL, 1 x 1 mL vials (AUST R 12301)

150 mg/1 mL, 1 x 1 mL vials (AUST R 12300)

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SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

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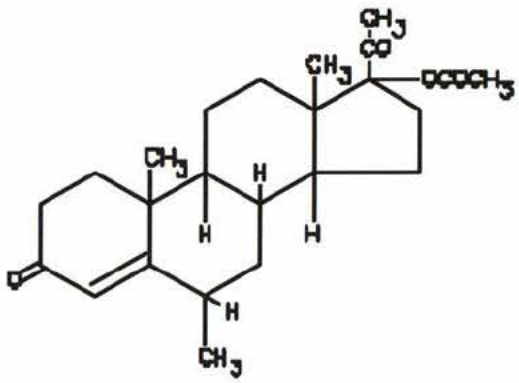
DEPO-RALOVERA®

Injection Suspension

(medroxyprogesterone acetate)

DESCRIPTION

Medroxyprogesterone acetate is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 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. Medroxyprogesterone acetate is 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate and its structural formula is as follows:



DEPO-RALOVERA injection suspension is supplied as 150 mg/1 mL vial. Each mL contains 150 mg medroxyprogesterone acetate, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and water for injections.

PHARMACOLOGY

Animal

Medroxyprogesterone acetate 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. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in

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recommended doses to women with adequate endogenous oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In five DEPO-RALOVERA clinical studies the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

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

Following a single 150 mg IM dose of DEPO-RALOVERA medroxyprogesterone acetate (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 intramuscular medroxyprogesterone acetate.

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

CLINICAL TRIALS

BMD Changes in Adult Women[3]

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

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

See WARNINGS.

BMD Changes in Adolescent Females (12-18 years)[5,6]

Preliminary results from an ongoing, open-label clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant

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decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See WARNINGS.

INDICATIONS

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

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

3. **Contraception (ovulation suppression):** For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see WARNINGS).[4]

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions

2. Markedly impaired liver function

3. Undiagnosed vaginal bleeding

4. Undiagnosed urinary tract bleeding

5. Undiagnosed breast pathology

6. Missed abortion

7. Known sensitivity to medroxyprogesterone acetate or any of the excipients - see DESCRIPTION

8. Known or suspected pregnancy - See PRECAUTIONS, Use in Pregnancy

9. Severe uncontrolled hypertension

10. Known or suspected malignancy of the breast (excluding use in oncology indications)

WARNINGS

1. **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.

2. **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.

3. **Bleeding Irregularities:** Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

   As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[38]

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

4. **Bone Mineral Changes:**

   Contraception and Endometriosis: Use of DEPO-RALOVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-RALOVERA is discontinued and ovarian oestrogen production increases.[4] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[6]

   DEPO-RALOVERA should only be used as a long-term (e.g. longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-RALOVERA long term.[4] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[4] Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-RALOVERA long-term, a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[4]

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

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis

See CLINICAL TRIALS.

Oncology: There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-RALOVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[23]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[23]

It is recommended that all patients have adequate calcium and Vitamin D intake.[7]

5. **Cancer Risks:** Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[9] and no increased overall risk of ovarian,[10] liver,[11] or cervical[12] cancer. There was a prolonged effect of reducing the risk of endometrial[13] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall relative risk of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89)[4] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[14] The risk of breast cancer[9] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[15] 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 Relative Risk of 2.19 thus increases the possible risk from 20.97 to

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45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

6. **Accidental Pregnancies:** Infants from accidental pregnancies that occur 1-2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[16,17]

   A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[18]

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

8. **Sexually Transmitted Diseases:** DEPO-RALOVERA is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

10. 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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

11. Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.

12. The following laboratory tests may be affected by the use of DEPO-RALOVERA:
    a. Gonadotrophin levels
    b. Plasma progesterone levels
    c. Urinary pregnanediol levels
    d. Plasma testosterone levels (in the male)

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e. Plasma oestrogen levels (in the female)

f. Plasma cortisol levels

g. Glucose Tolerance Test

h. Metyrapone Test - the use of medroxyprogesterone acetate 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.

i. Sex-hormone-binding-globulin concentrations are decreased.

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

13. **Drug Interactions:** Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of medroxyprogesterone acetate.[19] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

PRECAUTIONS

1. **Physical Examination:** The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

2. **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.

3. **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.

4. **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.

5. **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.

6. **Weight Changes:** There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kgs (136 lbs) women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kgs (5.4 lbs). Women who completed 2 years of therapy gained an average of 3.68 kgs (8.1 lbs). Women who completed 4 years gained an average of 6.3 kgs (13.8 lbs). Women who completed 6 years gained an average of 7.5 kgs (16.5 lbs). Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

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

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

9. **Hepatic Insufficiency:** 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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

10. **Patient Age:** The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.

11. **Pathology Tests:** The pathologist should be advised of progestin therapy when relevant specimens are submitted.

12. **IM Administration:** Gluteal infiltration and abscess formation may occur with intramuscular administration. The IM suspension is not formulated for subcutaneous injection. See DOSAGE AND ADMINISTRATION.

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

14. Medroxyprogesterone acetate used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in pregnancy: Category D

Studies in animals have shown that progestogens, including medroxyprogesterone acetate, 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

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

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

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

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

- during the first five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION)

(See also WARNINGS, item 6)

Use in lactation

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

Use in children

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[5,6] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.[4]

ADVERSE REACTIONS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

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1. Anaphylaxis, anaphylactoid-like reactions, angioedema

2. Cardiovascular - thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure

3. Central Nervous System - nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders

4. 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

5. Skin and mucous membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating

6. Gastro-intestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function

7. Breast – mastodynia, tenderness, galactorrhoea

8. Cervix - changes in the position of the transformation zone and in secretions

9. Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia

10. Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts

11. Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria

12. Genitourinary – prolonged anovulation

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- Menstrual irregularities (bleeding &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- Nervousness
- Headache
- Asthenia (weakness or fatigue)

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

- Decreased libido or anorgasmia

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- 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

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA[20,21,22].

DOSAGE AND ADMINISTRATION

Indications	Dosage
Inoperable, recurrent, metastatic, endometrial & renal carcinoma	Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by intramuscular injection for at least six months.
Contraception (ovulation suppression)	150 mg every 3 months by deep IM injection. To increase assurance that the patient is not pregnant at the

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	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[4]. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications[23].

Gluteal infiltration and abscess formation may occur with intramuscular 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 intra-muscular injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental oestrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the equivalent of 0.05 to 0.1 mg ethinyl estradiol 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.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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.

Contact the Poisons Information Centre for advice on the management of an overdose.

HOW SUPPLIED

DEPO-RALOVERA (medroxyprogesterone acetate) injection suspension is supplied as 150 mg/1 mL, 1 x 1 mL vials (AUST R 44464).

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SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

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PRODUCT INFORMATION

DEPO-PROVERA®

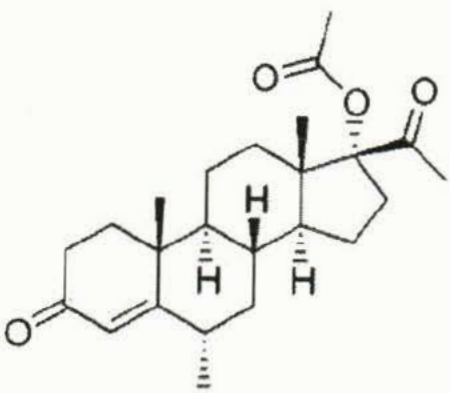
Injection Suspension

(medroxyprogesterone acetate)

DESCRIPTION

Medroxyprogesterone acetate is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 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.

Medroxyprogesterone acetate 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:



DEPO-PROVERA injection suspension is supplied in the following strengths and packages:

50 mg/1 mL vial - each mL contains 50 mg medroxyprogesterone acetate, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and water for injections.

150 mg/1 mL vial and syringe - each mL contains 150 mg medroxyprogesterone acetate, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and water for injections.

Please note presentations 50 mg/1 mL vial and 150 mg/1 mL syringe are not currently marketed in Australia.

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PHARMACOLOGY

Animal

Medroxyprogesterone acetate 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. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic 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 oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In five 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).[1,2] 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.

Pharmacokinetics

Parenteral medroxyprogesterone acetate 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 medroxyprogesterone acetate (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 intramuscular medroxyprogesterone acetate.

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

CLINICAL TRIALS

BMD Changes in Adult Women[3]

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 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 WARNINGS.

BMD Changes in Adolescent Females (12-18 years)[5, 6]

Preliminary results from an ongoing, open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See WARNINGS.

INDICATIONS

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

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

3. **Contraception (ovulation suppression):** For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-PROVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see WARNINGS).[4]

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-PROVERA 150 mg/1 mL, should be used for contraception.

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CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
2. Markedly impaired liver function
3. Undiagnosed vaginal bleeding
4. Undiagnosed urinary tract bleeding
5. Undiagnosed breast pathology
6. Missed abortion
7. Known sensitivity to medroxyprogesterone acetate or any of the excipients - see DESCRIPTION
8. Known or suspected pregnancy - See PRECAUTIONS, Use in Pregnancy
9. Severe uncontrolled hypertension
10. Known or suspected malignancy of the breast (excluding use in oncology indications)

WARNINGS

1. **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.
2. **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.
3. **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.[8]

   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.

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4. **Bone Mineral Changes:**

Contraception and Endometriosis: Use of DEPO-PROVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen 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 both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian oestrogen production increases.[4] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[6]

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.[4] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[4] Since loss of bone mineral density (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.[4]

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 CLINICAL TRIALS.

Oncology: There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, 2 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 CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-PROVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[23]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[23]

It is recommended that all patients have adequate calcium and Vitamin D intake.[7]

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5. **Cancer Risks:** Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[9] and no increased overall risk of ovarian,[10] liver,[11] or cervical[12] cancer. There was a prolonged effect of reducing the risk of endometrial[13] 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 relative risk of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89)[9] 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 relative risk increases in women aged between 25 and 34 years of age (RR: 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.[14] The risk of breast cancer[9] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[15] 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 Relative Risk 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 relative risk 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 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

6. **Accidental Pregnancies:** Infants from accidental pregnancies that occur 1-2 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.[16,17]

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.[18]

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

8. **Sexually Transmitted Diseases:** DEPO-PROVERA 150 mg/1 mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other

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sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

10. 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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

11. Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.

12. The following laboratory tests may be affected by the use of DEPO-PROVERA:
    a. Gonadotrophin levels
    b. Plasma progesterone levels
    c. Urinary pregnanediol levels
    d. Plasma testosterone levels (in the male)
    e. Plasma oestrogen levels (in the female)
    f. Plasma cortisol levels
    g. Glucose Tolerance Test
    h. Metyrapone Test - the use of medroxyprogesterone acetate 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.
    i. Sex-hormone-binding-globulin concentrations are decreased.
    j. Coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

13. **Drug Interactions:** Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of medroxyprogesterone acetate.[19] DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

PRECAUTIONS

1. **Physical Examination:** The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

2. **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.

3. **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.

4. **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.

5. **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.

6. **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 kgs (136 lbs) women who completed 1 year of therapy with DEPO-PROVERA gained an average of 2.45 kgs (5.4 lbs). Women who completed 2 years of therapy gained an average of 3.68 kgs (8.1 lbs). Women who completed 4 years gained an average of 6.3 kgs (13.8 lbs). Women who completed 6 years gained an average of 7.5 kgs (16.5 lbs). Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

7. **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.

8. **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.

9. ***Hepatic Insufficiency:** 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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

10. **Patient Age:** The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.

11. **Pathology Tests:** The pathologist should be advised of progestin therapy when relevant specimens are submitted.

12. **IM Administration:** Gluteal infiltration and abscess formation may occur with intramuscular administration. *The IM suspension is not formulated for subcutaneous injection. See DOSAGE AND ADMINISTRATION.

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13. 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.

14. Medroxyprogesterone acetate used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in pregnancy: Category D

Studies in animals have shown that progestogens, including medroxyprogesterone acetate, 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 medroxyprogesterone acetate in utero and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

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

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 five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION)

(See also WARNINGS, item 6)

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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.

Use in children

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[5,6] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for postmenarcheal adolescent and adult females.[4]

ADVERSE REACTIONS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

1. Anaphylaxis, anaphylactoid-like reactions, angioedema
2. Cardiovascular - thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
3. Central Nervous System - nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
4. 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
5. Skin and mucous membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
6. Gastrointestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
7. Breast – mastodynia, tenderness, galactorrhoea
8. Cervix - changes in the position of the transformation zone and in secretions
9. Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
10. Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts

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11. Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria

12. Genitourinary – prolonged anovulation

In a clinical trial conducted using DEPO-PROVERA for contraception over 3900 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 &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- 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

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, *confusion, *euphoria, *loss of concentration, convulsions, changes in appetite, *vomiting, gastrointestinal disturbances, jaundice, *cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia,

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*cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

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[20,21,22].

DOSAGE AND ADMINISTRATION

Indications	Dosage
Inoperable, recurrent, metastatic, endometrial & renal carcinoma	Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by intramuscular injection for at least six 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.

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-PROVERA 150 mg/1 mL, should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years[4]. An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications[23].

Gluteal infiltration and abscess formation may occur with intramuscular 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 intra-muscular injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental oestrogens 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 oestrogens in the

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equivalent of 0.05 to 0.1 mg ethinyl estradiol 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.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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.

Contact the Poisons Information Centre for advice on the management of an overdose.

HOW SUPPLIED

DEPO-PROVERA (medroxyprogesterone acetate) injection suspension is supplied as:

50 mg/1 mL, 1 x 1 mL vials (AUST R 12301)#

150 mg/1 mL, 1 x 1 mL vials (AUST R 12300)

150 mg/1 mL, 1 x 1 mL syringe (AUST R 12279)#

Not currently marketed in Australia,

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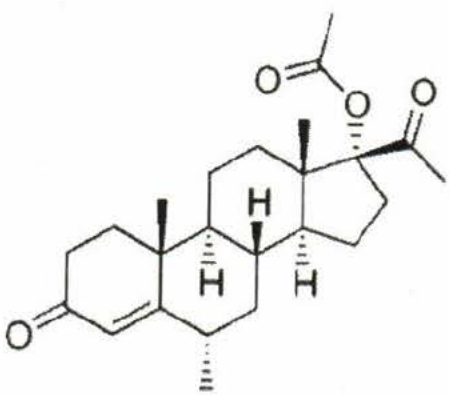
PRODUCT INFORMATION

DEPO-RALOVERA®
Injection Suspension
(medroxyprogesterone acetate)

DESCRIPTION

Medroxyprogesterone acetate is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 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.

Medroxyprogesterone acetate 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:



DEPO-RALOVERA injection suspension is supplied in the following strengths and packages:

50 mg/1 mL vial - each mL contains 50 mg medroxyprogesterone acetate, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and water for injections.

150 mg/1 mL vial - each mL contains 150 mg medroxyprogesterone acetate, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and water for injections.

Please note presentation 50 mg/1 mL vial is not currently marketed in Australia.

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PHARMACOLOGY

Animal

Medroxyprogesterone acetate 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. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In five DEPO-RALOVERA clinical studies the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

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

Following a single 150 mg IM dose of DEPO-RALOVERA medroxyprogesterone acetate (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 intramuscular medroxyprogesterone acetate.

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

CLINICAL TRIALS

BMD Changes in Adult Women[3]

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean BMD decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more

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

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

See WARNINGS.

BMD Changes in Adolescent Females (12-18 years)[5, 6]

Preliminary results from an ongoing, open-label clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See WARNINGS.

INDICATIONS

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

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

3. **Contraception (ovulation suppression):** For long-term prevention of pregnancy in women when administered at 3-month intervals.

Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see WARNINGS).[4]

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The 150 mg/1 mL, should be used for contraception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions

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2. Markedly impaired liver function

3. Undiagnosed vaginal bleeding

4. Undiagnosed urinary tract bleeding

5. Undiagnosed breast pathology

6. Missed abortion

7. Known sensitivity to medroxyprogesterone acetate or any of the excipients - see DESCRIPTION

8. Known or suspected pregnancy - See PRECAUTIONS, Use in Pregnancy

9. Severe uncontrolled hypertension

10. Known or suspected malignancy of the breast (excluding use in oncology indications)

WARNINGS

1. **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.

2. **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.

3. **Bleeding Irregularities:** Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

   As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[38]

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

4. **Bone Mineral Changes:**

   Contraception and Endometriosis: Use of DEPO-RALOVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism

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accommodates to a lower oestrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-RALOVERA is discontinued and ovarian oestrogen production increases.[4] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[6]

DEPO-RALOVERA should only be used as a long-term (e.g. longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-RALOVERA long term.[4] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[4] Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-RALOVERA long-term, a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[4]

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

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g, anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis

See CLINICAL TRIALS.

Oncology: There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-RALOVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[23]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[23]

It is recommended that all patients have adequate calcium and Vitamin D intake.[7]

5. **Cancer Risks:** Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[9] and no

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increased overall risk of ovarian,[10] liver,[11] or cervical[12] cancer. There was a prolonged effect of reducing the risk of endometrial[13] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall relative risk of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89)[4] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[14] The risk of breast cancer[9] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[15] 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 Relative Risk of 2.19 thus increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

6. **Accidental Pregnancies:** Infants from accidental pregnancies that occur 1-2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[16,17]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[18]

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

8. **Sexually Transmitted Diseases:** DEPO-RALOVERA 150 mg/1 mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

10. 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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

11. Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.

12. The following laboratory tests may be affected by the use of DEPO-RALOVERA:
    a. Gonadotrophin levels
    b. Plasma progesterone levels
    c. Urinary pregnanediol levels
    d. Plasma testosterone levels (in the male)
    e. Plasma oestrogen levels (in the female)
    f. Plasma cortisol levels
    g. Glucose Tolerance Test
    h. Metyrapone Test - the use of medroxyprogesterone acetate 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.
    i. Sex-hormone-binding-globulin concentrations are decreased.
    j. Coagulation test values for prothrombin (Factor II) and Factors VII, VIII, IX and X may increase.

13. **Drug Interactions:** Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of medroxyprogesterone acetate.[19] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

PRECAUTIONS

1. **Physical Examination:** The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

2. **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.

3. **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.

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4. **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.

5. **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.

6. **Weight Changes:** There is a tendency for women to gain weight while on DEPO-RALOVERA therapy. From an initial average body weight of 61.8 kgs (136 lbs) women who completed 1 year of therapy with DEPO-RALOVERA gained an average of 2.45 kgs (5.4 lbs). Women who completed 2 years of therapy gained an average of 3.68 kgs (8.1 lbs). Women who completed 4 years gained an average of 6.3 kgs (13.8 lbs). Women who completed 6 years gained an average of 7.5 kgs (16.5 lbs). Two per cent of women withdrew from a large-scale clinical trial because of excessive weight gain.

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

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

9. ***Hepatic Insufficiency:** 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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

10. **Patient Age:** The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.

11. **Pathology Tests:** The pathologist should be advised of progestin therapy when relevant specimens are submitted.

12. **IM Administration:** Gluteal infiltration and abscess formation may occur with intramuscular administration. *The IM suspension is not formulated for subcutaneous injection. See DOSAGE AND ADMINISTRATION.

13. Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-RALOVERA is not recommended

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for treatment for secondary amenorrhoea or dysfunctional uterine bleeding. In these conditions, oral therapy is recommended.

14. Medroxyprogesterone acetate used in the treatment of cancer patients may produce Cushingoid symptoms.

Use in pregnancy: Category D

Studies in animals have shown that progestogens, including medroxyprogesterone acetate, 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 medroxyprogesterone acetate in utero and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

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

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

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

- during the first five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION)

(See also WARNINGS, item 6)

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Use in lactation

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

Use in children

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[5,6] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.[4]

ADVERSE REACTIONS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

1. Anaphylaxis, anaphylactoid-like reactions, angioedema
2. Cardiovascular - thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
3. Central Nervous System - nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
4. 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
5. Skin and mucous membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
6. Gastro-intestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
7. Breast – mastodynia, tenderness, galactorrhoea
8. Cervix - changes in the position of the transformation zone and in secretions
9. Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
10. Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts

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11. Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria

12. Genitourinary – prolonged anovulation

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- Menstrual irregularities (bleeding &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- Nervousness
- Headache
- Asthenia (weakness or fatigue)

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

- Decreased libido or anorgasmia
- Vaginitis
- Backache
- Pelvic pain
- Leg cramps
- Breast pain
- Depression
- No hair growth or alopecia
- Nausea
- Bloating
- Insomnia
- Rash
- Leukorrhoea
- Oedema/*fluid retention
- Acne
- Hot flushes

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, *confusion, *euphoria, *loss of concentration, convulsions, changes in appetite, *vomiting, gastrointestinal disturbances, jaundice, *cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia,

*cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA[20,21,22].

DOSAGE AND ADMINISTRATION

Indications	Dosage
Inoperable, recurrent, metastatic, endometrial & renal carcinoma	Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by intramuscular injection for at least six 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.

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The 150 mg/1 mL, should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years[4]. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications[23].

Gluteal infiltration and abscess formation may occur with intramuscular 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 intra-muscular injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental oestrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the

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equivalent of 0.05 to 0.1 mg ethinyl estradiol 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.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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.

Contact the Poisons Information Centre for advice on the management of an overdose.

HOW SUPPLIED

DEPO-RALOVERA (medroxyprogesterone acetate) injection suspension is supplied as:

50 mg/1 mL, 1 x 1 mL vials (AUST R 44463) #

150 mg/1 mL, 1 x 1 mL vials (AUST R 44464).

Not currently marketed in Australia,

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SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

Approved by Therapeutic Goods Administration: 2 May 1995

Date of most recent amendment: xxxxxx 25 AUG 2011

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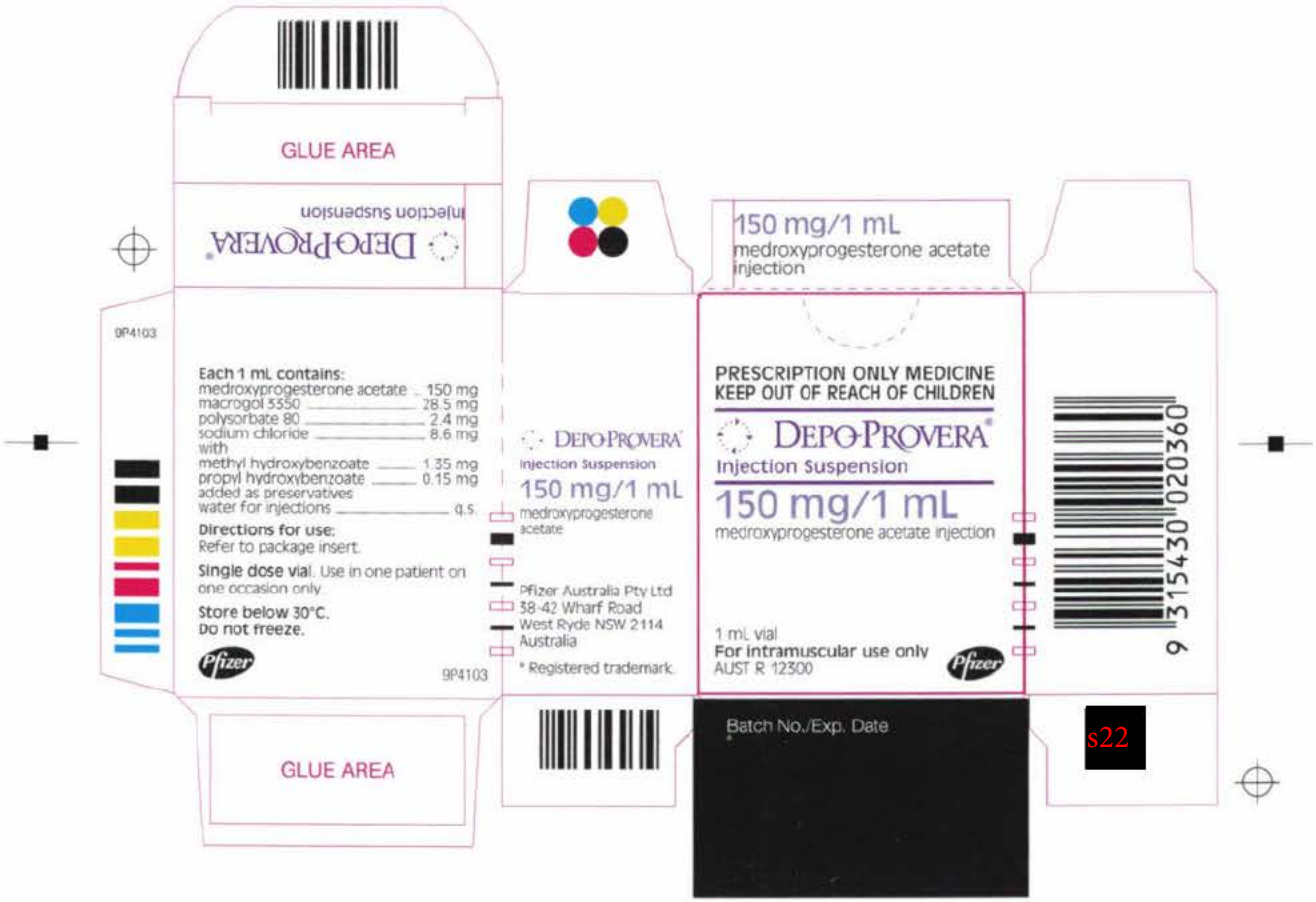
GLUE AREA
DEPO-PROVERA®
injection suspension
9P4103
Each 1 mL contains:
medroxyprogesterone acetate 150 mg
macrogol 3350 28.5 mg
polysorbate 80 2.4 mg
sodium chloride 8.6 mg
with
methyl hydroxybenzoate 1.35 mg
propyl hydroxybenzoate 0.15 mg
added as preservatives
water for injections q.s.
Directions for use:
Refer to package insert.
Single dose vial. Use in one patient on one occasion only.
Store below 30°C.
Do not freeze.
9P4103
DEPO-PROVERA®
injection suspension
150 mg/1 mL
medroxyprogesterone acetate
Pfizer Australia Pty Ltd
38-42 Wharf Road
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® Registered trademark.
150 mg/1 mL
medroxyprogesterone acetate injection
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
DEPO-PROVERA®
Injection Suspension
150 mg/1 mL
medroxyprogesterone acetate injection
1 mL vial
For intramuscular use only
AUST R 12300
9 315430 020360
GLUE AREA
Batch No./Exp. Date
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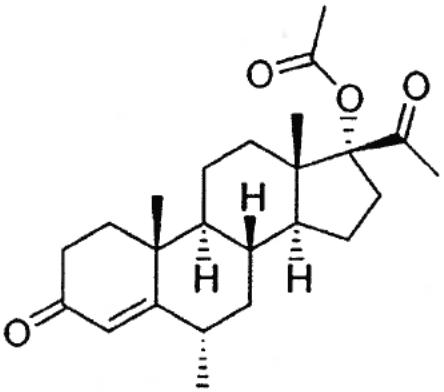
PRODUCT INFORMATION

DEPO-PROVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

Medroxyprogesterone acetate is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 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.

DEPO-PROVERA injection suspension is supplied in the following strengths and packages:

50 mg/1 mL vial - each mL contains 50 mg medroxyprogesterone acetate, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and Water for Injections.

150 mg/1 mL vial and syringe - each mL contains 150 mg medroxyprogesterone acetate, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Animal

Medroxyprogesterone acetate 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. Medroxyprogesterone acetate induces glandular development in the

endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic 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 oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In five 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).[1,2] 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.

Pharmacokinetics

Parenteral medroxyprogesterone acetate 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 medroxyprogesterone acetate 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 intramuscular medroxyprogesterone acetate.

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

CLINICAL TRIALS

BMD Changes in Adult Women[3]

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 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 PRECAUTIONS.

BMD Changes in Adolescent Females (12-18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also

[redacted] s22

showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

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 bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-PROVERA 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 bone mineral density (see PRECAUTIONS).[6]

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-PROVERA 150 mg/1 mL, should be used for contraception.

CONTRAINDICATIONS

- 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 medroxyprogesterone acetate or any of the excipients (see DESCRIPTION)
- Known or suspected pregnancy (see PRECAUTIONS, Use in Pregnancy
- Severe uncontrolled hypertension
- Known or suspected malignancy of the breast (excluding use in oncology indications).

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PRECAUTIONS

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.

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.[7]

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 Changes

Contraception and Endometriosis

Use of DEPO-PROVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen 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 both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[5]

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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-PROVERA long-term (greater than 2 years), a risk/benefit

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assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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 CLINICAL TRIALS.

Oncology

There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO-PROVERA for oncology use.

However, 2 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 CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-PROVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer Risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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 relative risk of breast cancer associated with the use of DEPO-PROVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89) [6] 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 relative risk increases in women aged between 25 and 34 years of age (RR: 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.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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 Relative Risk 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 relative risk 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 1.22 to 1.28 and 95% CI 0.93-1.70). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Accidental Pregnancies

Infants from accidental pregnancies that occur 1-2 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.[17,18]

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.[19]

Ectopic Pregnancy

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

Sexually Transmitted Diseases

DEPO-PROVERA 150 mg/1 mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortison blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

Anaphylactic and Anaphylactoid Reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.

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

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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 progestins 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 intramuscular administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

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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.

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

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 medroxyprogesterone acetate, may have an adverse effect on the developing foetus, including teratogenicity and foetotoxicity.

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

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female foetuses. 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 foetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female foetus and because of the increased association of hypospadias in the male foetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

Children exposed to medroxyprogesterone acetate 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 foetus.

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 five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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

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medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

Paediatric Use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

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 oestrogen levels (in the female)
- Plasma cortisol levels
- Glucose Tolerance Test
- Metyrapone Test - the use of medroxyprogesterone acetate 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of medroxyprogesterone acetate.[20] DEPO-PROVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Medroxyprogesterone acetate (MPA) is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur. Combined use of MPA with CYP3A4 inhibitors or inducers may result in compromised efficacy due to decreased systemic levels of MPA.

ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- Cardiovascular - thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- Central Nervous System - nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- 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
- Skin and mucous membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- Gastrointestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- Breast – mastodynia, tenderness, galactorrhoea
- Cervix - changes in the position of the transformation zone and in secretions
- Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- Genitourinary – prolonged anovulation.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3900 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 &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- 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.

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

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.[21,22,23]

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by intramuscular injection for at least six 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.

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

#The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-PROVERA 150 mg/1 mL, should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

Gluteal infiltration and abscess formation may occur with intramuscular 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 intra-muscular injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental oestrogens 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 oestrogens in the equivalent of 0.05 to 0.1 mg ethinyl estradiol 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.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentations

DEPO-PROVERA (medroxyprogesterone acetate) injection suspension is supplied as:

50 mg/1 mL, 1 x 1 mL vials[#]

150 mg/1 mL, 1 x 1 mL vials

150 mg/1 mL, 1 x 1 mL syringe .[#]

These presentations are not currently available in Australia.

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Storage Conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

dd mmm 2013.

® Registered trademark

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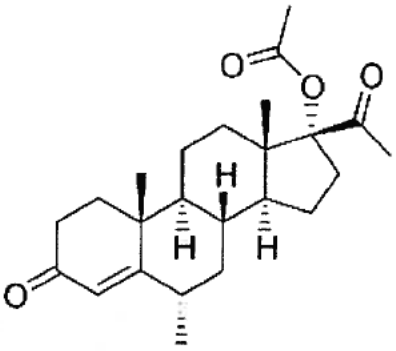
PRODUCT INFORMATION

DEPO-RALOVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

Medroxyprogesterone acetate is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200 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.

DEPO-RALOVERA injection suspension is supplied in the following strengths and packages:

50 mg/1 mL vial - each mL contains 50 mg medroxyprogesterone acetate, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and Water for Injections.

150 mg/1 mL vial and syringe - each mL contains 150 mg medroxyprogesterone acetate, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Animal

Medroxyprogesterone acetate 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. Medroxyprogesterone acetate induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous

cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In five DEPO-RALOVERA clinical studies the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

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

Following a single 150 mg IM dose of DEPO-RALOVERA medroxyprogesterone acetate 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 intramuscular medroxyprogesterone acetate.

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

CLINICAL TRIALS

BMD Changes in Adult Women[3]

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

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

See PRECAUTIONS.

BMD Changes in Adolescent Females (12-18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from

baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

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 bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (see PRECAUTIONS).[6]

The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-RALOVERA 150 mg/1 mL, should be used for contraception.

CONTRAINDICATIONS

- 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 medroxyprogesterone acetate or any of the excipients (see DESCRIPTION)
- Known or suspected pregnancy (see PRECAUTIONS, Use in Pregnancy)
- Severe uncontrolled hypertension
- Known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

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.

Ocular Disorders

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

Bleeding Irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[7]

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

Bone Mineral Changes

Contraception and Endometriosis

Use of DEPO-RALOVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-RALOVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[5]

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-RALOVERA long term.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a

risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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

- Chronic alcohol and/or tobacco use
- Chronic use of drugs that can reduce bone mass, e.g., anticonvulsants or corticosteroids
- Low body mass index or eating disorder, e.g., anorexia nervosa or bulimia
- Metabolic bone disease
- Strong family history of osteoporosis.

See CLINICAL TRIALS.

Oncology

There are no studies on the bone mineral density (BMD) effects of high doses of parenteral DEPO-RALOVERA for oncology use.

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-RALOVERA may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer Risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall relative risk of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased relative risk of 2.19 (95% CI 1.23-3.89)[6] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The relative risk increases in women aged between 25 and 34 years of age (RR: 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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 Relative Risk 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.

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

Accidental Pregnancies

Infants from accidental pregnancies that occur 1-2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic Pregnancy

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

Sexually Transmitted Diseases

DEPO-RALOVERA 150 mg/1 mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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. Medroxyprogesterone acetate may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that medroxyprogesterone acetate possesses adrenocorticoid activity.

Anaphylactic and Anaphylactoid Reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with intramuscular medroxyprogesterone acetate.

Fluid Retention

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

Breakthrough Bleeding

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

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

Carbohydrate Metabolism

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

CNS Disorders and Convulsions

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

Weight Changes

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

Return of Fertility

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

Liver Function

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

Patient Age

The age of the patient constitutes no absolute limiting factor although treatment with progestins 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 intramuscular administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

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General

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

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

Use in Pregnancy: Pregnancy Category D

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

Studies in animals have shown that progestogens, including medroxyprogesterone acetate, may have an adverse effect on the developing foetus, including teratogenicity and foetotoxicity.

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

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female foetuses. 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 foetuses, but because some of these drugs induce mild virilisation of the external genitalia of the female foetus and because of the increased association of hypospadias in the male foetus, it is prudent to avoid use of these drugs during the first trimester of pregnancy.

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

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

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

- during the first five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

Use in Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA, milk composition, quality and amount are not adversely affected. Infants exposed to

medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

Paediatric Use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

Effects on Laboratory Tests

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

- Gonadotrophin levels
- Plasma progesterone levels
- Urinary pregnanediol levels
- Plasma testosterone levels (in the male)
- Plasma oestrogen levels (in the female)
- Plasma cortisol levels
- Glucose Tolerance Test
- Metyrapone Test - the use of medroxyprogesterone acetate 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of medroxyprogesterone acetate.[20] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

Medroxyprogesterone acetate (MPA) is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers of CYP3A4 on MPA have not been conducted or reported in the literature, physicians should consider that interactions could occur. Combined use of MPA with CYP3A4 inhibitors or inducers may result in compromised efficacy due to decreased systemic levels of MPA.

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ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone.

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- Cardiovascular - thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- Central Nervous System - nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- 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
- Skin and mucous membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- Gastrointestinal/hepatobiliary – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- Breast – mastodynia, tenderness, galactorrhoea
- Cervix - changes in the position of the transformation zone and in secretions
- Miscellaneous - hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- Metabolic and nutritional – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- Genitourinary – prolonged anovulation.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- Menstrual irregularities (bleeding &/or amenorrhoea)
- Abdominal pain or discomfort
- Dizziness
- Weight changes
- Nervousness
- Headache
- Asthenia (weakness or fatigue).

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

- Decreased libido or anorgasmia
- Vaginitis
- Backache
- Pelvic pain

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- Leg cramps
- Breast pain
- Depression
- No hair growth or alopecia
- Nausea
- Bloating
- Insomnia
- Rash
- Leukorrhoea
- Oedema/fluid retention
- Acne
- Hot flushes.

Events reported by fewer than 1% of subjects included: galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.[21,22,23]

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by intramuscular injection for at least six 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.

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

#The 50 mg/1 mL vial is not approved for the indication of contraception (ovulation suppression). The injection, DEPO-RALOVERA 150 mg/1 mL, should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.[8]

Gluteal infiltration and abscess formation may occur with intramuscular 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 intra-muscular injection into the gluteal muscle.

Routine or long-term cyclic use of supplemental oestrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the equivalent of 0.05 to 0.1 mg ethinyl estradiol 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.

OVERDOSAGE

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

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of medroxyprogesterone acetate 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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

DEPO-RALOVERA (medroxyprogesterone acetate) injection suspension is supplied as:
50 mg/1 mL, 1 x 1 mL vials#
150 mg/1 mL, 1 x 1 mL vials
150 mg/1 mL, 1 x 1 mL syringe. #

These presentations are not currently available in Australia.

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Storage Conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 May 1993.

DATE OF MOST RECENT AMENDMENT

dd mmm 2013.

® Registered trademark

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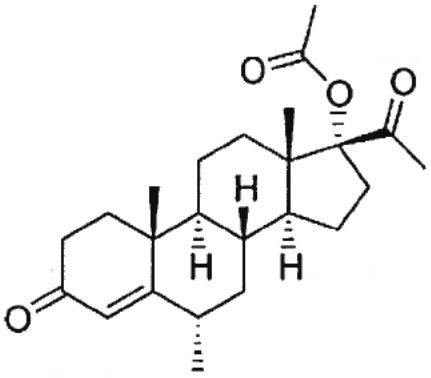
PRODUCT INFORMATION

DEPO-PROVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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 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.

DEPO-PROVERA 50 mg/mL injection suspension contains 50 mg MPA, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and Water for Injections.

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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 oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In

[redacted]

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 oestrogen, 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 five 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).[1,2] 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.

Pharmacokinetics

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.

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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 PRECAUTIONS.

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BMD changes in adolescent females (12-18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women, who use DEPO-PROVERA 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 PRECAUTIONS).[6]

The DEPO-PROVERA 50 mg/mL vial presentation is not approved for the indication of contraception (ovulation suppression). The DEPO-PROVERA 150 mg/mL vial and syringe presentation should be used for contraception.

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 DESCRIPTION)

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- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

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.

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.[7]

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 oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen 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 both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[5]

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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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] 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.[6]

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 CLINICAL TRIALS.

Oncology

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

However, 2 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 CLINICAL TRIALS). Decreases in serum oestrogen 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.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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)[6] 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.[15] The risk of

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breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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 1-2 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.[17,18]

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.[19]

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 diseases

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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.

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Fluid retention

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

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.

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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 DOSAGE AND 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 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 five days after the onset of a normal menstrual period
- within five 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

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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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

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 oestrogen 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.

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INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of MPA.[20] 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.

ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone:

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- *Cardiovascular* – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- *Central Nervous System* – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- *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
- *Skin and mucous membranes* – urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- *Gastrointestinal/hepatobiliary* – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- *Breast* – mastodynia, tenderness, galactorrhoea
- *Cervix* – changes in the position of the transformation zone and in secretions
- *Miscellaneous* – hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- *Metabolic and nutritional* – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- *Genitourinary* – prolonged anovulation.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3900 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) [redacted] s22

- abdominal pain or discomfort
- dizziness
- weight changes
- 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.

Events reported by fewer than 1% of subjects included galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

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.[21,22,23]

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DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by IM injection for at least six 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.

The DEPO-PROVERA 50 mg/mL vial presentation is not approved for the indication of contraception (ovulation suppression). The DEPO-PROVERA 150 mg/mL vial and syringe presentation should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

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 oestrogens 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 oestrogens in the equivalent of 0.05 to 0.1 mg ethinyloestradiol 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.

OVERDOSAGE

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

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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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentations

DEPO-PROVERA (medroxyprogesterone acetate) injection suspension is supplied as:
50 mg/mL, 1 x 1 mL vials#
150 mg/mL, 1 x 1 mL vials
150 mg/mL, 1 x 1 mL syringe.#

#These presentations are not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

Dd mmm 2014.

® Registered trademark

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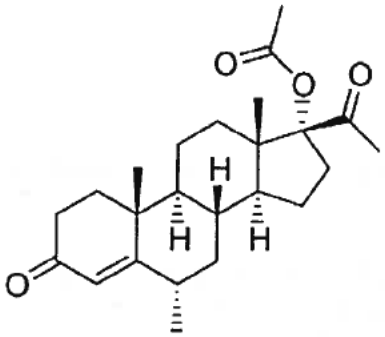
PRODUCT INFORMATION

DEPO-RALOVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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 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.

DEPO-RALOVERA 50 mg/L injection suspension contains 50 mg MPA, 28.8 mg macrogol 3350, 8.6 mg sodium chloride, 1.9 mg polysorbate 80, 1.3 mg methyl hydroxybenzoate, 0.14 mg propyl hydroxybenzoate and Water for Injections.

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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 oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

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Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous oestrogen, 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 five DEPO-RALOVERA clinical studies the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

Absorption

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

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

Metabolism

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

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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

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

See PRECAUTIONS.

BMD changes in adolescent females (12-18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also

showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see PRECAUTIONS).[6]

The DEPO-RALOVERA 50 mg/mL vial presentation is not approved for the indication of contraception (ovulation suppression). The DEPO-RALOVERA 150 mg/mL vial and syringe presentation should be used for contraception.

CONTRAINDICATIONS

DEPO-RALOVERA is contraindicated in patients with:

- thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- markedly impaired liver function
- undiagnosed vaginal bleeding
- undiagnosed urinary tract bleeding
- undiagnosed breast pathology
- missed abortion
- known sensitivity to MPA or any of the excipients in the injection (see DESCRIPTION)
- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension

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- known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

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.

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[7]

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

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-RALOVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[5]

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-RALOVERA long term.[6] In adolescent females, interpretation of BMD results should

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take into account patient age and skeletal maturity.[6] Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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

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

See CLINICAL TRIALS.

Oncology

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

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)[6] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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

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RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1-2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic pregnancy

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

Sexually transmitted diseases

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

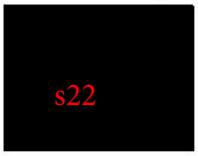
Clinical suppression of adrenocorticoid function has not been observed at low dose levels, however at the high doses used in the treatment of cancer, corticoid-like activity has been reported. MPA may decrease adrenocorticotrophic hormone and hydrocortisone blood levels. Animal studies show that MPA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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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



Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

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IM Administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

General

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

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

Use in Pregnancy: Category D

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

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

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

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

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

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

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

- during the first five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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Use in lactation

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

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

Effects on laboratory tests

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

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma oestrogen 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[20] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

MPA is metabolised *in-vitro* primarily by hydroxylation via the CYP3A4. While specific drug-drug interaction studies evaluating the clinical effect of CYP3A4 inhibitors or inducers on

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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.

ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone:

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- *Cardiovascular* – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- *Central Nervous System* – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- *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
- *Skin and mucous membranes* – urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- *Gastrointestinal/hepatobiliary* – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- *Breast* – mastodynia, tenderness, galactorrhoea
- *Cervix* – changes in the position of the transformation zone and in secretions
- *Miscellaneous* – hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- *Metabolic and nutritional* – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- *Genitourinary* – prolonged anovulation.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

- menstrual irregularities (bleeding and/or amenorrhoea)
- abdominal pain or discomfort
- dizziness
- weight changes
- nervousness
- headache

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- asthenia (weakness or fatigue).

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

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

Events reported by fewer than 1% of subjects included galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.[21,22,23]

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

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

Breast carcinoma

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

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Endometriosis

50 mg weekly or 100 mg every two weeks by IM injection for at least six 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.

The DEPO-RALOVERA 50 mg/mL vial presentation is not approved for the indication of contraception (ovulation suppression). The DEPO-RALOVERA 150 mg/mL vial and syringe presentation should be used for contraception.

BMD should be evaluated when considering contraceptive or endometriotic treatment beyond 2 years.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.[8]

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 oestrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the equivalent of 0.05 to 0.1 mg ethinyloestradiol 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.

OVERDOSAGE

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA (medroxyprogesterone acetate) 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.

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Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

DEPO-RALOVERA (medroxyprogesterone acetate) injection suspension is supplied as:
50 mg/ mL, 1 x 1 mL vials#
150 mg/ mL, 1 x 1 mL vials
150 mg/ mL, 1 x 1 mL syringe.#

These presentations are not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 May 1993.

DATE OF MOST RECENT AMENDMENT

Dd mmm 2014.

® Registered trademark.

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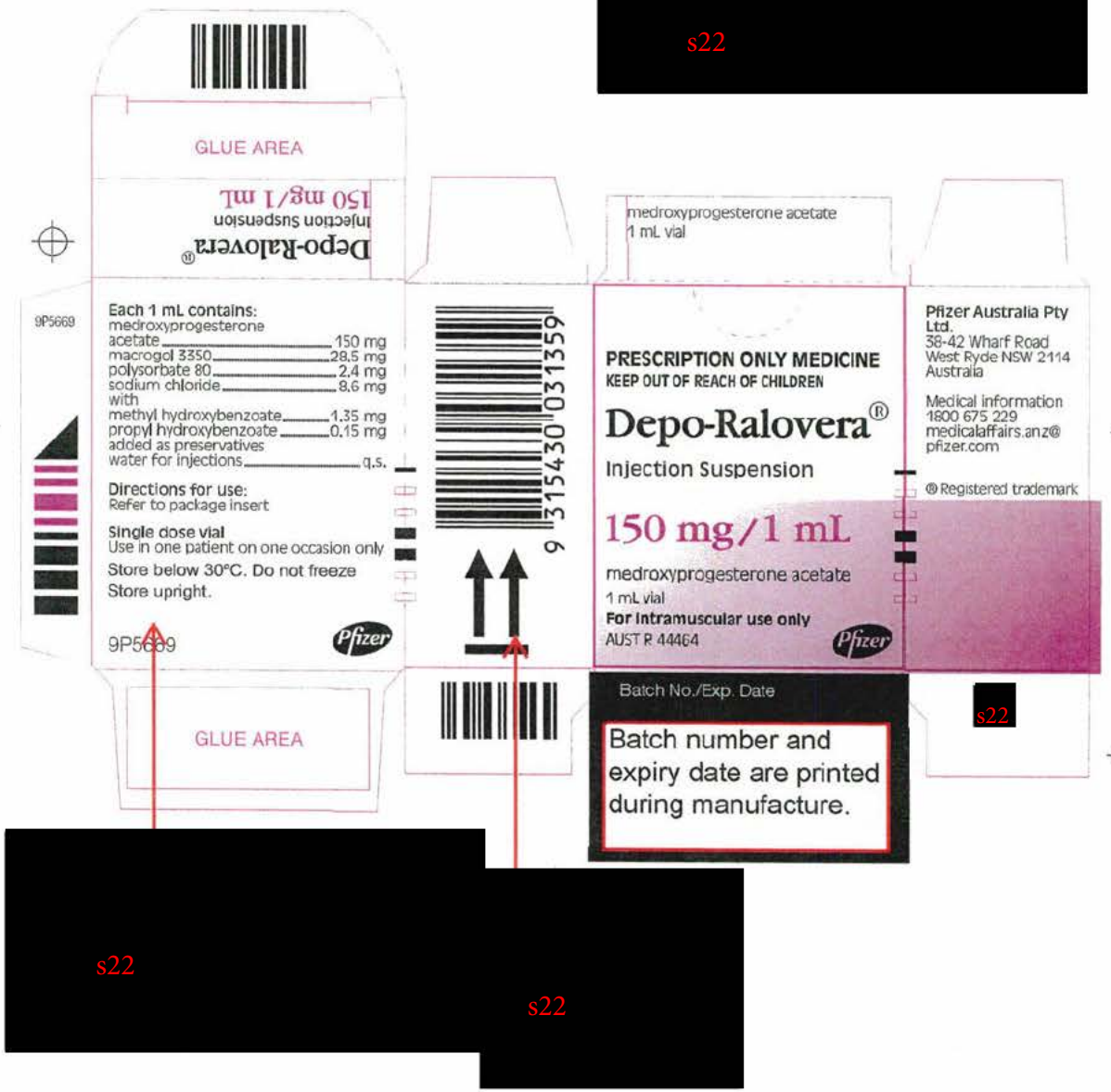

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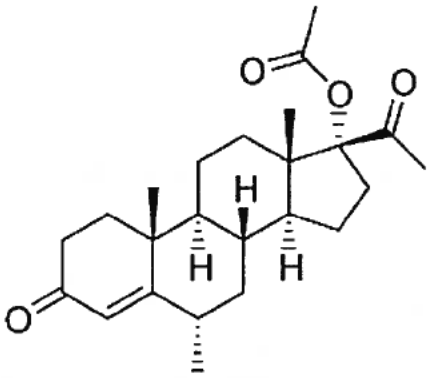
PRODUCT INFORMATION

DEPO-PROVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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 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.

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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 oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

[redacted]

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 oestrogen, 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 five 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).[1,2] 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.

Pharmacokinetics

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.

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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 PRECAUTIONS.

BMD changes in adolescent females (12-18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also

showed that DEPO-PROVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women, who use DEPO-PROVERA 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 PRECAUTIONS).[6]

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 DESCRIPTION)
- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

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PRECAUTIONS

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.

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.[7]

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 oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen 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 both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[5]

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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] Since loss of BMD may occur in pre-menopausal women who use DEPO-PROVERA long-term (greater than 2 years), a

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risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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 CLINICAL TRIALS.

Oncology

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

However, 2 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 CLINICAL TRIALS). Decreases in serum oestrogen 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.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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)[6] 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.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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.

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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 1-2 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.[17,18]

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.[19]

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 diseases

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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.

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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 DOSAGE AND 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

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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 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 five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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.

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Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 CONTRAINDICATIONS).

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 oestrogen 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of MPA.[20] 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.

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ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone:

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- *Cardiovascular* – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- *Central Nervous System* – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- *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
- *Skin and mucous membranes* – urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- *Gastrointestinal/hepatobiliary* – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- *Breast* – mastodynia, tenderness, galactorrhoea
- *Cervix* – changes in the position of the transformation zone and in secretions
- *Miscellaneous* – hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- *Metabolic and nutritional* – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- *Genitourinary* – prolonged anovulation.

In a clinical trial conducted using DEPO-PROVERA for contraception over 3900 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 changes
- 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.

Events reported by fewer than 1% of subjects included galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

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.[21,22,23]

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 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 two weeks by IM injection for at least six months.

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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.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

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 oestrogens 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 oestrogens in the equivalent of 0.05 to 0.1 mg ethinyloestradiol 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.

OVERDOSAGE

No serious medical effects have been reported in association with overdosage of DEPO-PROVERA (medroxyprogesterone acetate) 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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentations

DEPO-PROVERA (medroxyprogesterone acetate) 150 mg/mL injection suspension is supplied as:

- 1 x 1 mL vial

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- 1 x 1 mL syringe.#

#This presentation is not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

dd mmm 2014.

® Registered trademark

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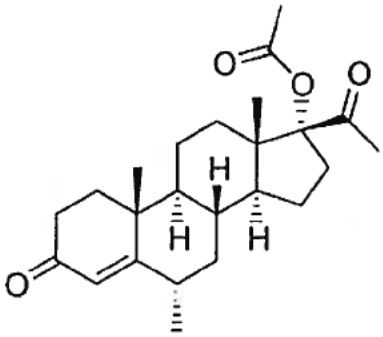
PRODUCT INFORMATION

DEPO-RALOVERA®

(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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 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.

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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 oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended

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doses to women with adequate endogenous oestrogen, 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 five DEPO-RALOVERA clinical studies the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

Absorption

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

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

Metabolism

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

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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

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

See PRECAUTIONS.

BMD changes in adolescent females (12-18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12-18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent

girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see PRECAUTIONS).[6]

CONTRAINDICATIONS

DEPO-RALOVERA is contraindicated in patients with:

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

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PRECAUTIONS

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.

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[7]

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

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-RALOVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing.[5]

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-RALOVERA long term.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a

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risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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

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

See CLINICAL TRIALS.

Oncology

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

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)[6] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1-2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic pregnancy

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

Sexually transmitted diseases

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM Administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

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General

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

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

Use in Pregnancy: Category D

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

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

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

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

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

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

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

- during the first five days after the onset of a normal menstrual period
- within five 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA,

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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.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12-18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 metabolized in patients with severe liver insufficiency (see CONTRAINDICATIONS).

Effects on laboratory tests

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

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma oestrogen 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[20] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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

[redacted] s22

CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone:

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- *Cardiovascular* – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- *Central Nervous System* – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- *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
- *Skin and mucous membranes* – urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- *Gastrointestinal/hepatobiliary* – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- *Breast* – mastodynia, tenderness, galactorrhoea
- *Cervix* – changes in the position of the transformation zone and in secretions
- *Miscellaneous* – hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- *Metabolic and nutritional* – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- *Genitourinary* – prolonged anovulation.

In a clinical trial conducted using DEPO-RALOVERA for contraception over 3900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of DEPO-RALOVERA. The following adverse reactions were reported by more than 5% of subjects:

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

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

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

Events reported by fewer than 1% of subjects included galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.[21,22,23]

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

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

Breast carcinoma

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

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Endometriosis

50 mg weekly or 100 mg every two weeks by IM injection for at least six 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.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.[8]

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 oestrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the equivalent of 0.05 to 0.1 mg ethinyloestradiol 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.

OVERDOSAGE

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA (medroxyprogesterone acetate) 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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

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PRESENTATION AND STORAGE CONDITIONS

Presentation

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

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 May 1993.

DATE OF MOST RECENT AMENDMENT

dd mmm 2014.

® Registered trademark.

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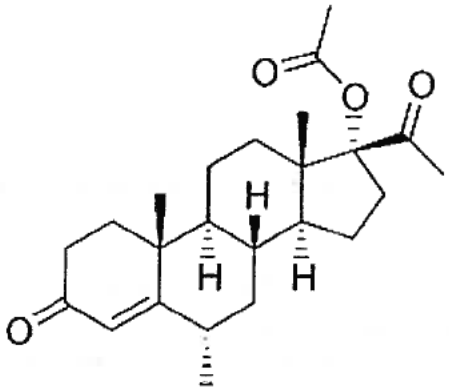
PRODUCT INFORMATION

DEPO-PROVERA®

(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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.

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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 oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

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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 oestrogen, 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).[1,2] 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.

Pharmacokinetics

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.

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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 PRECAUTIONS.

BMD changes in adolescent females (12 to 18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for up to 5 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. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women, who use DEPO-PROVERA 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 PRECAUTIONS).[6]

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 DESCRIPTION)
- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

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PRECAUTIONS

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.

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.[7]

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 oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen 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 both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian oestrogen production increases.[6] A study to assess the reversibility of loss of BMD in adolescent females is ongoing. [5]

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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] Since loss of BMD may occur in pre-menopausal women who use DEPO-PROVERA long-term (greater than 2 years), a

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risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered. [6]

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 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 CLINICAL TRIALS). Decreases in serum oestrogen 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. [8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term. [8]

It is recommended that all patients have adequate calcium and Vitamin D intake. [9]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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)[6] 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.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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.

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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.[17,18]

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.[19]

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 diseases

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

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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 DOSAGE AND ADMINISTRATION).

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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 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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

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exposed to medroxyprogesterone via breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-PROVERA are expected to be the same for postmenarcheal adolescent and adult females. [6]

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 CONTRAINDICATIONS).

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 oestrogen 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of MPA.[20] 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.

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ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone:

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- *Cardiovascular* – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- *Central Nervous System* – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- *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
- *Skin and mucous membranes* – urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- *Gastrointestinal/hepatobiliary* – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- *Breast* – mastodynia, tenderness, galactorrhoea
- *Cervix* – changes in the position of the transformation zone and in secretions
- *Miscellaneous* – hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- *Metabolic and nutritional* – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- *Genitourinary* – prolonged anovulation.

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 changes
- 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

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- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

Events reported by fewer than 1% of subjects included galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

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.[21,22,23]

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

DOSAGE AND 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.

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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.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

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 oestrogens 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 oestrogens in the equivalent of 0.05 mg to 0.1 mg ethinyloestradiol 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.

OVERDOSAGE

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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

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

- 1 x 1 mL vial

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- 1 x 1 mL syringe.#

#This presentation is not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

dd Month YYYY.

® Registered trademark

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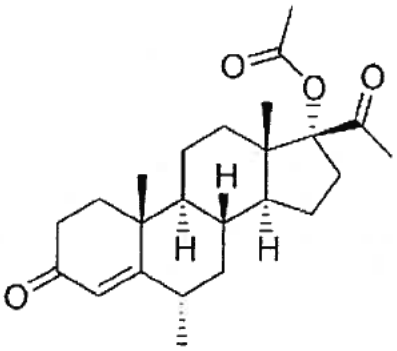
PRODUCT INFORMATION

DEPO-RALOVERA®

(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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.

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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 oestrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant oestrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended

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doses to women with adequate endogenous oestrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

Absorption

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

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

Metabolism

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

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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

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

See PRECAUTIONS.

BMD changes in adolescent females (12 to 18 years)[4,5]

Preliminary results from an ongoing, open-label clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4.2% after 5 years; mean decreases for the total hip and femoral neck were 6.9% and 6.1%, respectively. In contrast, most

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adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

See PRECAUTIONS.

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see PRECAUTIONS).[6]

CONTRAINDICATIONS

DEPO-RALOVERA is contraindicated in patients with:

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

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PRECAUTIONS

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.

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[7]

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

Bone mineral density changes

Contraception and endometriosis

Use of DEPO-RALOVERA reduces serum oestrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower oestrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-RALOVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-RALOVERA is discontinued and ovarian oestrogen production increases.6 A study to assess the reversibility of loss of BMD in adolescent females is ongoing.5

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when a female needs to continue to use DEPO-RALOVERA long term.6 In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.6 Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a

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risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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

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

See CLINICAL TRIALS.

Oncology

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

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum oestrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)6 has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic pregnancy

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

Sexually transmitted diseases

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

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General

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

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

Use in pregnancy: Category D

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

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

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

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

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

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

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

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

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

See DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

Use in lactation

Detectable amounts of drug have been identified in the milk of mothers receiving DEPO-RALOVERA. In mothers who are breastfeeding and who are treated with DEPO-RALOVERA,

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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.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4,5] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.[6]

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 CONTRAINDICATIONS).

Effects on laboratory tests

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

- gonadotrophin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma oestrogen 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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[20] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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

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CYP3A4 inducers may result in decreased systemic levels of MPA whilst co-administration with CYP3A4 inhibitors may result in increased MPA levels.

ADVERSE EFFECTS

The following events listed in order of seriousness rather than frequency of occurrence, have been associated with the use of progestogens including medroxyprogesterone:

- Anaphylaxis, anaphylactoid-like reactions, angioedema
- *Cardiovascular* – thromboembolic disease, thrombophlebitis, pulmonary embolism, palpitations, retinal thrombosis, cerebral and myocardial infarction, congestive heart failure
- *Central Nervous System* – nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, tremor, vision disorders
- *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
- *Skin and mucous membranes* – urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating
- *Gastrointestinal/hepatobiliary* – nausea, constipation, diarrhoea, dry mouth, disturbed liver function
- *Breast* – mastodynia, tenderness, galactorrhoea
- *Cervix* – changes in the position of the transformation zone and in secretions
- *Miscellaneous* – hyperpyrexia, Cushing Syndrome, weight gain, injection site reactions, arthralgia, malaise, hypercalcaemia
- Moderate elevation of blood pressure, transient elevations of alkaline phosphatase and/or serum transaminase activities, elevations of serum calcium and potassium levels, and increases in white cell and platelet counts
- *Metabolic and nutritional* – decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
- *Genitourinary* – prolonged anovulation.

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

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

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

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

Events reported by fewer than 1% of subjects included galactorrhoea, melasma, chloasma, confusion, euphoria, loss of concentration, convulsions, changes in appetite, vomiting, gastrointestinal disturbances, jaundice, cholestatic icterus, genitourinary infections, vaginal cysts, dyspareunia, paraesthesia, chest pain, pulmonary embolus, allergic reactions, anaemia, drowsiness, syncope, dyspnoea and asthma, tachycardia, fever, excessive, sweating and body odour, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer, prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical erosions, cervical cancer, varicose veins, dysmenorrhoea, hirsutism, accidental pregnancy, thrombophlebitis, deep vein thrombosis.

Post-marketing experience

In post-marketing experience, there have been reports of anaphylactic responses, thromboembolic events and rare cases of osteoporosis including osteoporotic fractures reported in patients taking DEPO-RALOVERA.[21,22,23]

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

DOSAGE AND 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.

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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.6 An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.8

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 oestrogens with DEPO-RALOVERA is not recommended. Excessive or prolonged bleeding which becomes troublesome to the patient can usually be controlled by the administration of oral or parenteral oestrogens in the equivalent of 0.05 mg to 0.1 mg ethinyloestradiol 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.

OVERDOSAGE

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

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

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

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Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

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

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 May 1993.

DATE OF MOST RECENT AMENDMENT

dd Month YYYY.

® Registered trademark.

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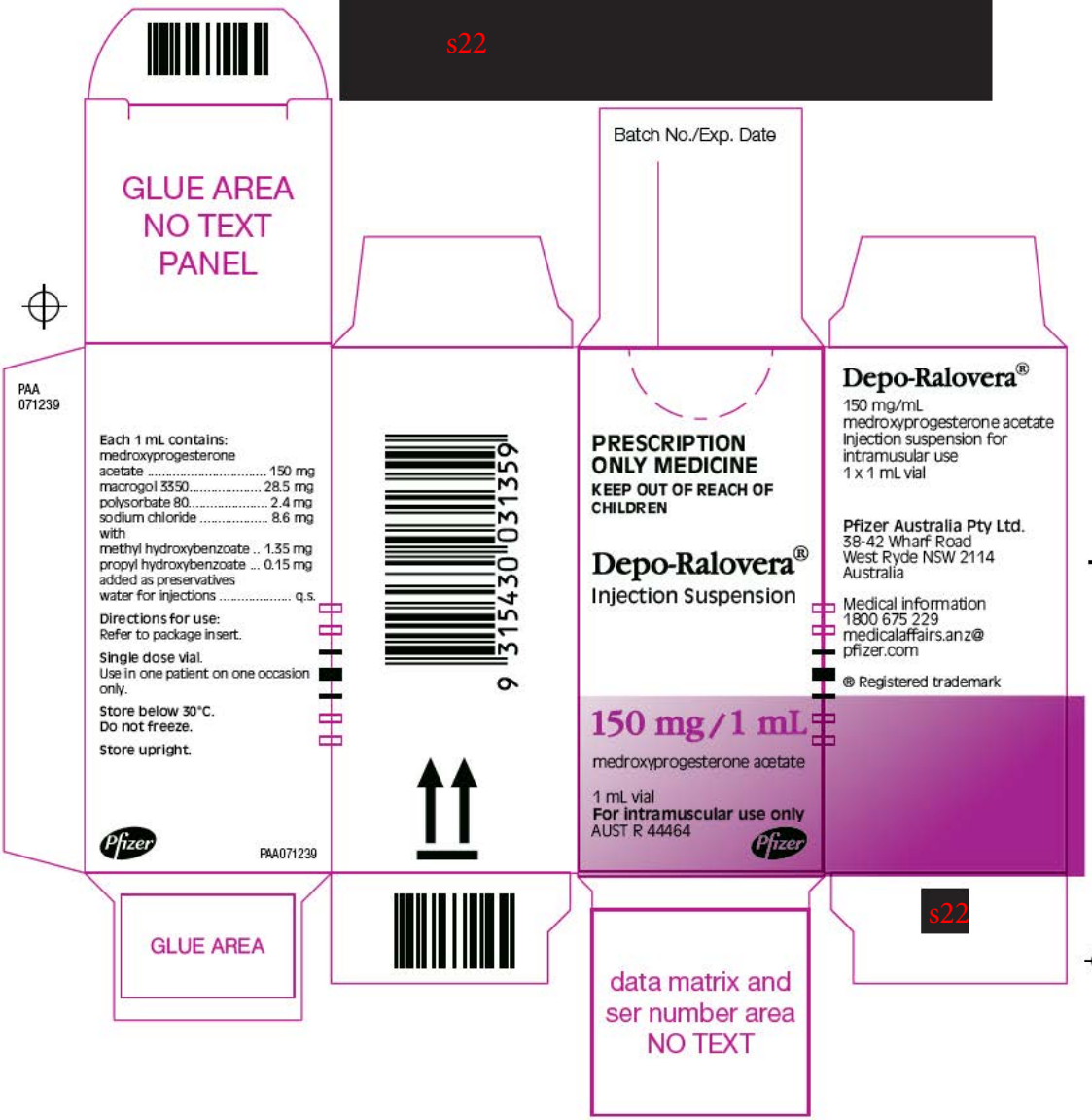

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Each 1 mL contains:
medroxyprogesterone
acetate ..... 150 mg
macrogol 3350..... 28.5 mg
polysorbate 80..... 2.4 mg
sodium chloride ..... 8.6 mg
with
methyl hydroxybenzoate .. 1.35 mg
propyl hydroxybenzoate ... 0.15 mg
added as preservatives
water for injections ..... q.s.

Directions for use:
Refer to package insert.

Single dose vial. Use in one patient on one occasion only.

Store below 30°C. Do not freeze.
Store upright.

Pfizer

PAA071237

DEPO-PROVERA®
Injection Suspension
150 mg/1 mL
medroxyprogesterone acetate

For intramuscular use only
1 x 1 mL vial

Pfizer Australia Pty Ltd
38-42 Wharf Road
West Ryde NSW 2114
Australia

® Registered trademark.

Batch No./Exp. Date

PRESCRIPTION ONLY
MEDICINE
KEEP OUT OF REACH OF
CHILDREN

DEPO-PROVERA®
Injection Suspension
150 mg/1 mL
medroxyprogesterone acetate
injection

1 mL vial
For intramuscular use only
AUST R 12300

Pfizer

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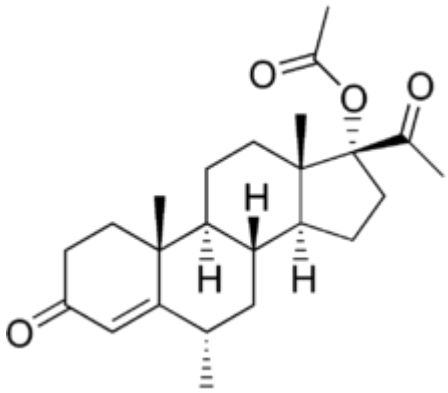
PRODUCT INFORMATION

DEPO-PROVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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.

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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).[1,2] 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.

Pharmacokinetics

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.

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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 PRECAUTIONS.

BMD changes in adolescent females (12 to 18 years)[4,5]

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 year after treatment was discontinued and hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued (see PRECAUTIONS).

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women, who use DEPO-PROVERA 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 PRECAUTIONS).[6]

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 DESCRIPTION)
- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

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.

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.[7]

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.[6] Full recovery took 1 year at the lumbar spine and approximately 3 years for total hip after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see 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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] 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.[6]

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 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 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.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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)[6] 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.[15] The risk of

breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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.[17,18]

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.[19]

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 DOSAGE AND 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 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4,5] (see 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. [6]

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 CONTRAINDICATIONS).

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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of MPA.[20] 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.

ADVERSE 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.[21,22,23]

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.

DOSAGE AND 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.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

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.

OVERDOSAGE

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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

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

- 1 x 1 mL vial
- 1 x 1 mL syringe.[#]

[#]This presentation is not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

DD Month YYYY.

® Registered trademark

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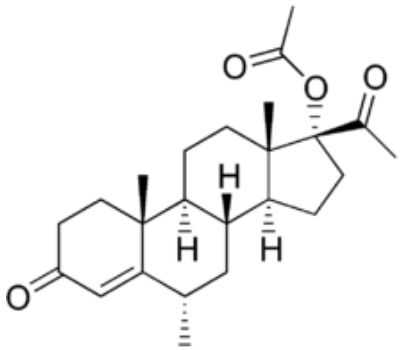
PRODUCT INFORMATION

DEPO-RALOVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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.

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Animal

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

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended

doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

Absorption

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

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

Metabolism

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

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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

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

BMD changes in adolescent females (12 to 18 years)[4,5]

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

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued, hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued (see PRECAUTIONS).

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see PRECAUTIONS).[6]

CONTRAINDICATIONS

DEPO-RALOVERA is contraindicated in patients with:

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

PRECAUTIONS

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.

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[7]

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

Bone mineral density changes

Contraception and endometriosis

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

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

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases.6 Full recovery took 1 year for the lumbar spine and approximately 3 years for total hip after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see CLINICAL TRIALS, BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when DEPO-RALOVERA is used long term.6 In adolescent females, interpretation of BMD results should take into account patient age

and skeletal maturity.6 Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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

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

See CLINICAL TRIALS.

Oncology

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

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)6 has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A

RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic pregnancy

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

Sexually transmitted infections

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

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

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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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

Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

General

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

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

Use in pregnancy: Category D

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

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

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

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

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

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

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

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

When switching from other contraceptive methods, MPA IM should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both

methods, (e.g., patients switching from oral contraceptives should have their first injection of MPA within 7 days after taking their last active pill).

See DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

Use in lactation

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

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.

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 CONTRAINDICATIONS).

Effects on laboratory tests

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

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

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[20] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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

ADVERSE EFFECTS

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

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

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

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

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

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

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

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

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

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

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

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

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-RALOVERA.[21,22,23]

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.

DOSAGE AND 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.6 An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.8

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

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

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

OVERDOSAGE

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

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

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

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

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

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 May 1993.

DATE OF MOST RECENT AMENDMENT

DD Month YYYY.

® Registered trademark.

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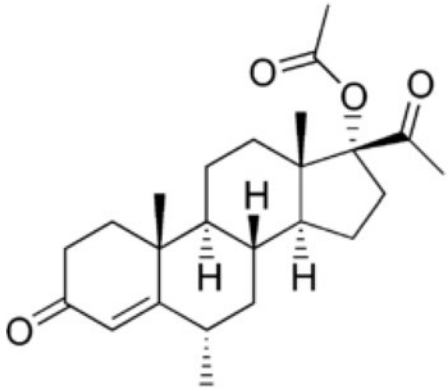
PRODUCT INFORMATION

DEPO-PROVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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.

DEPO-PROVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

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).[1,2] 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.

Pharmacokinetics

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.

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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 PRECAUTIONS.

BMD changes in adolescent females (12 to 18 years)[4,5]

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 year after treatment was discontinued and hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued (see PRECAUTIONS).

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women, who use DEPO-PROVERA 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 PRECAUTIONS).[6]

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 DESCRIPTION)
- known or suspected pregnancy (see PRECAUTIONS, Use in pregnancy)
- severe uncontrolled hypertension
- known or suspected malignancy of the breast (excluding use in oncology indications).

PRECAUTIONS

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.

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.[7]

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.[6] Full recovery took 1 year at the lumbar spine and approximately 3 years for total hip after discontinuation of treatment. Longer duration of treatment and smoking were associated with slower recovery (see 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.[6] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[6] 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.[6]

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 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 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.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] 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)[6] 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.[15] The risk of

breast cancer[10] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] 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.[17,18]

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.[19]

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 diseases

DEPO-PROVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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 DOSAGE AND 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 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 DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

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.

Paediatric use

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4,5] (see 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. [6]

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 CONTRAINDICATIONS).

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.

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly decrease the serum concentration of MPA.[20] 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.

ADVERSE 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.[21,22,23]

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.

DOSAGE AND 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.[6] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[8]

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.

OVERDOSAGE

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.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

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

- 1 x 1 mL vial
- 1 x 1 mL syringe.[#]

[#]This presentation is not currently available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 August 1991.

DATE OF MOST RECENT AMENDMENT

dd mmm 2016.

® Registered trademark

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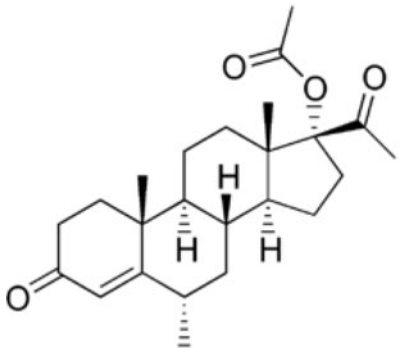
PRODUCT INFORMATION

DEPO-RALOVERA®
(medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (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:



DESCRIPTION

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.

DEPO-RALOVERA 150 mg/mL injection suspension contains 150 mg MPA, 28.5 mg macrogol 3350, 8.6 mg sodium chloride, 2.4 mg polysorbate 80, 1.35 mg methyl hydroxybenzoate, 0.15 mg propyl hydroxybenzoate and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Animal

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

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended

doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[1,2] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Pharmacokinetics

Absorption

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

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

Metabolism

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

CLINICAL TRIALS

Bone mineral density changes in adult women[3]

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

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

BMD changes in adolescent females (12 to 18 years)[4,5]

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

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued, hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued (see PRECAUTIONS).

INDICATIONS

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see PRECAUTIONS).[6]

CONTRAINDICATIONS

DEPO-RALOVERA is contraindicated in patients with:

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

PRECAUTIONS

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.

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[7]

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

Bone mineral density changes

Contraception and endometriosis

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

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

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases.6 Full recovery took 1 year for the lumbar spine and approximately 3 years for total hip after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see CLINICAL TRIALS, BMD changes in adolescent females (12 to 18 years)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated when DEPO-RALOVERA is used long term.6 In adolescent females, interpretation of BMD results should take into account patient age

and skeletal maturity.6 Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[6]

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

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

See CLINICAL TRIALS.

Oncology

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

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see CLINICAL TRIALS). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[8]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term.[8]

It is recommended that all patients have adequate calcium and Vitamin D intake.[9]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[10] and no increased overall risk of ovarian,[11] liver,[12] or cervical cancer.[13] There was a prolonged effect of reducing the risk of endometrial[14] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)6 has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[15] The risk of breast cancer[10] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[16] report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A

RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[17,18]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[19]

Ectopic pregnancy

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

Sexually transmitted diseases

DEPO-RALOVERA 150 mg/mL is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases. The woman should be advised that additional measures are needed to prevent the transmission of sexually transmitted diseases.

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

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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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

Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

Gluteal infiltration and abscess formation may occur with IM administration. The IM suspension is not formulated for subcutaneous injection (see DOSAGE AND ADMINISTRATION).

General

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

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

Use in pregnancy: Category D

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

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

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

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

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

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

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

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

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

See DOSAGE AND ADMINISTRATION. See also PRECAUTIONS.

Use in lactation

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

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[4] (see CLINICAL TRIALS). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.

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 CONTRAINDICATIONS).

Effects on laboratory tests

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

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

INTERACTIONS WITH OTHER MEDICINES

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[20] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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

ADVERSE EFFECTS

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

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

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

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

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

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

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

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

- decreased libido or anorgasmia
- vaginitis
- backache
- pelvic pain
- leg cramps
- breast pain
- depression
- no hair growth or alopecia
- nausea
- bloating
- insomnia
- rash
- leukorrhoea
- oedema/fluid retention
- acne
- hot flushes.

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

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

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

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-RALOVERA.[21,22,23]

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.

DOSAGE AND 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.6 An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.8

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

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

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

OVERDOSAGE

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

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

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

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

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

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

POISON SCHEDULE

S4, Prescription Only Medicine.

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31 May 1993.

DATE OF MOST RECENT AMENDMENT

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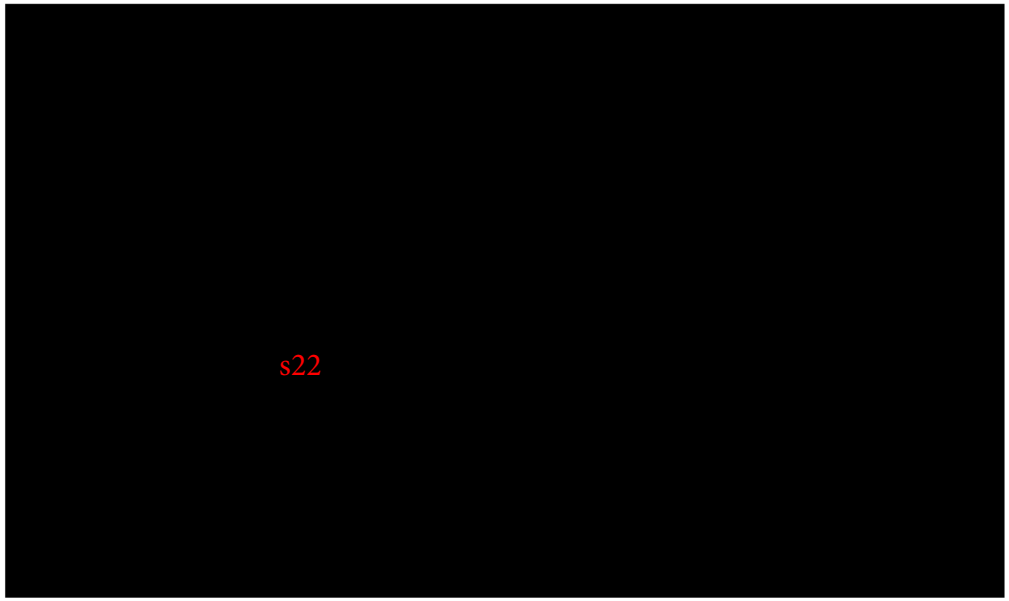
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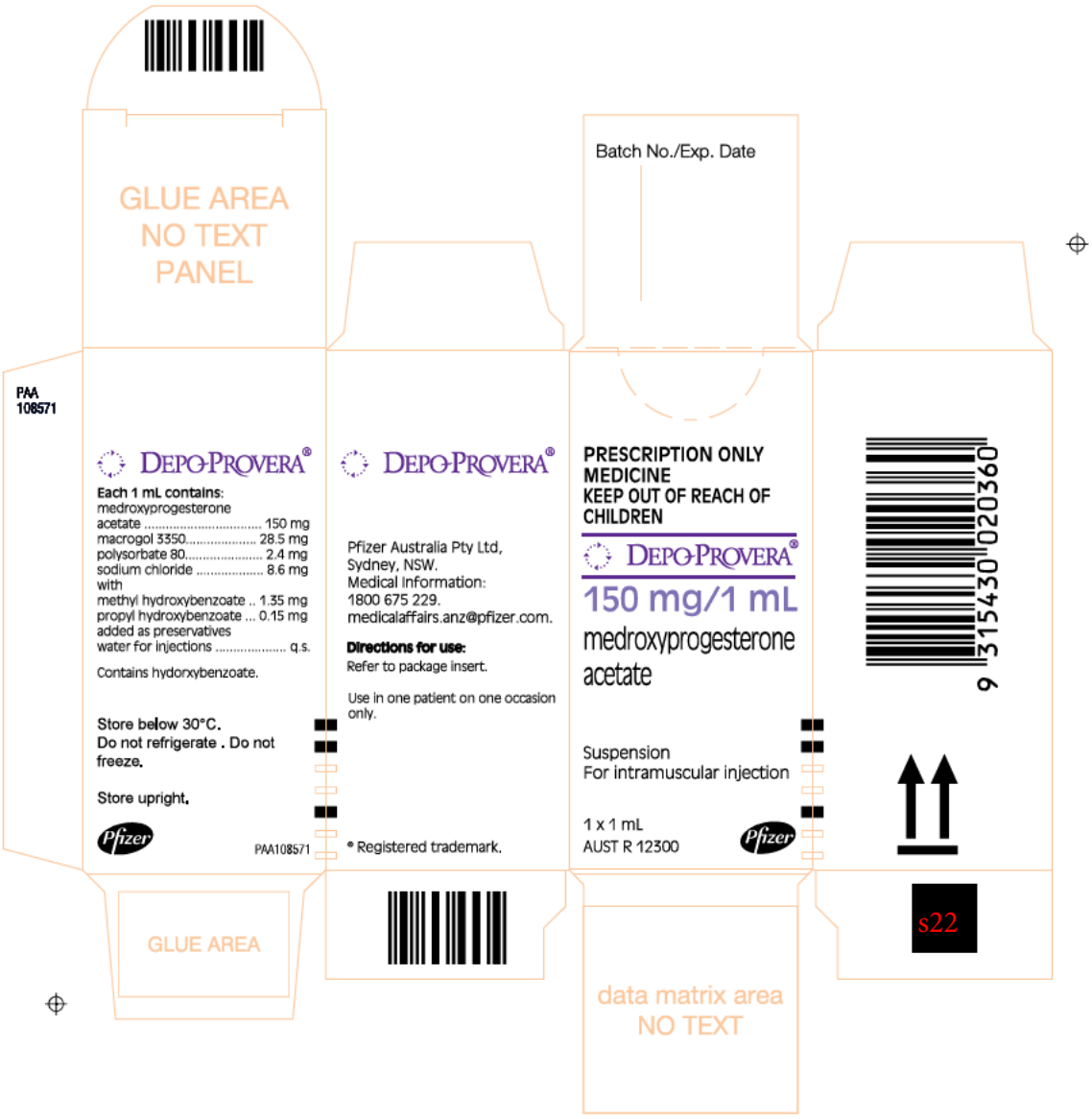
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Depo-Ralovera®
150 mg/1 mL
medroxyprogesterone acetate
Suspension
For intramuscular injection
1 x 1 mL vial
AUST R 44464
Depo-Ralovera®
Pfizer Australia Pty Ltd
Sydney, NSW.
Medical information:
1800 675 229
medical affairs.anz@pfizer.com
Directions for use:
Refer to package insert.
Use in one patient on one occasion only.
s22
GLUE AREA
data matrix area
NO TEXT

[redacted]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DEPO-PROVERA®
Each 1 mL contains:
medroxyprogesterone
acetate ..... 150 mg
macrogol 3350..... 28.5 mg
polysorbate 80..... 2.4 mg
sodium chloride ..... 8.6 mg
with
methyl hydroxybenzoate .. 1.35 mg
propyl hydroxybenzoate ... 0.15 mg
added as preservatives
water for injections ..... q.s.
Contains hydorxybenzoate.
Store below 30°C.
Do not refrigerate . Do not freeze.
Store upright.
PAA108571
DEPO-PROVERA®
Pfizer Australia Pty Ltd,
Sydney, NSW.
Medical Information:
1800 675 229.
medicalaffairs.anz@pfizer.com.
Directions for use:
Refer to package insert.
Use in one patient on one occasion only.
® Registered trademark.
PRESCRIPTION ONLY
MEDICINE
KEEP OUT OF REACH OF
CHILDREN
DEPO-PROVERA®
150 mg/1 mL
medroxyprogesterone
acetate
Suspension
For intramuscular injection
1 x 1 mL
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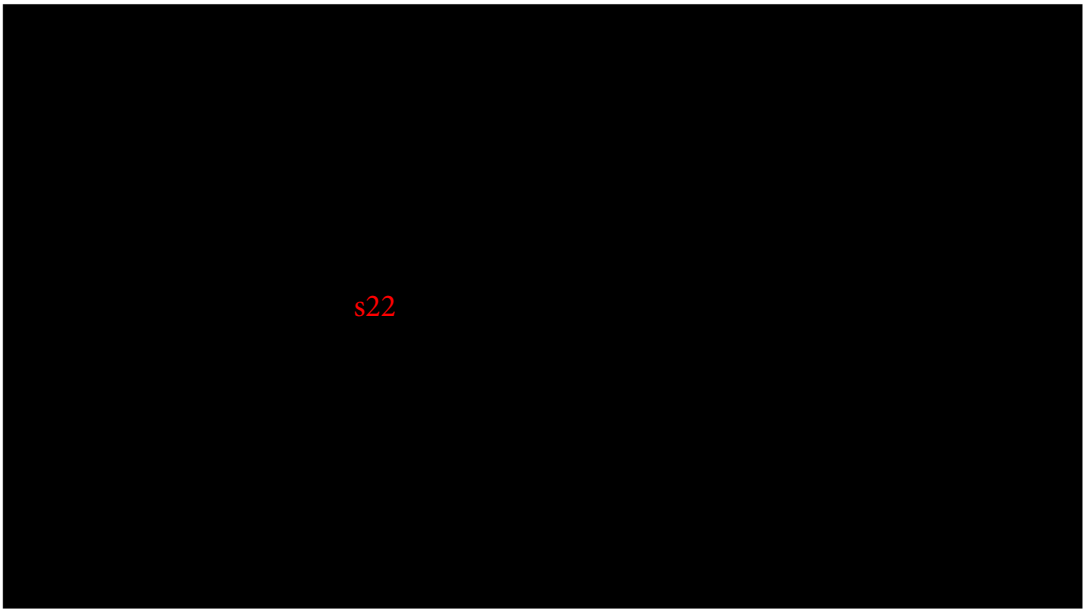

s22

Batch No./Exp. Date
Depo-Ralovera®
150 mg/1 mL
medroxyprogesterone acetate
Suspension
For IM injection only
1 mL vial
PAA108844

s22

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).[1]

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.[1] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[2]

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.

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.[3]

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.[1] Full recovery took 1 year at the lumbar spine and approximately 3 years for total hip 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.[1] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[1] 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.[1]

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.[2]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term. [2]

It is recommended that all patients have adequate calcium and Vitamin D intake.[4]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[6] and no increased overall risk of ovarian,[6] liver,[7] or cervical cancer.[8] There was a prolonged effect of reducing the risk of endometrial[9] 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)[1] 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.[11] The risk of breast cancer[6] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[11] 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.[12,13]

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.[14]

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)[15,16] (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.[1]

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.[17] 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.[18,19,20]

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).[21,22] 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[23]

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)[15,16]

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 year after treatment was discontinued and hip BMD recovered to baseline levels approximately 3 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 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 syringe.[#]

[#]This presentation is not currently available in Australia.

6.6 Special precautions for disposal

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

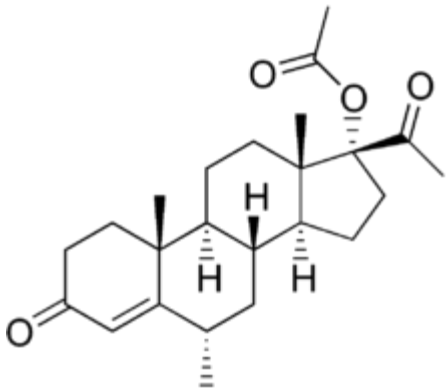
6.7 Physicochemical properties

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.pfizer.com.au

9. DATE OF FIRST APPROVAL

2 August 1991.

10. DATE OF REVISION

TBC.

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
All	Reformat to SmPC format

2; 3; 4; 5; & 6	Editorial
7	CAS number added
8	Sponsor details updated

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

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium

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

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).[1]

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.[1] An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.[2]

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

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

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

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

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

4.4 Special warnings and precautions for use

Physical examination

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

Thromboembolic disorders

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

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of

women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[3]

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

Bone mineral density changes

Contraception and endometriosis

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

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

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases.[1] Full recovery took 1 year at the lumbar spine and approximately 3 years for total hip after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated DEPO-RALOVERA is used long term.[1] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[1] Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[1]

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

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

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

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

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[2]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term. [2]

It is recommended that all patients have adequate calcium and Vitamin D intake.[4]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[5] and no increased overall risk of ovarian,[6] liver,[7] or cervical cancer.[8] There was a prolonged effect of reducing the risk of endometrial[9] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)[1] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[10] The risk of breast cancer[5] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[11] report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[12,13]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[14]

Ectopic pregnancy

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

Sexually transmitted infections

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

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

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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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

Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

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

General

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

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[15] (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.

Effects on laboratory tests

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

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

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[16] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions – Return of fertility

Use in pregnancy – Pregnancy Category D

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

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

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

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

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

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

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

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

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

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

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

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

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

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

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

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

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

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

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

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

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

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

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

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

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-RALOVERA.[17,18,19]

There have been post-marketing reports of lipodystrophy acquired.

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

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

Reporting suspected adverse effects

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

4.9 Overdose

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

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

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with

DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[20.21] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Clinical trials

Bone mineral density changes in adult women[22]

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

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

BMD changes in adolescent females (12 to 18 years)[15, 23]

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

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1 year after treatment was discontinued, hip BMD recovered to baseline levels approximately 3 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

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

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

Metabolism

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

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

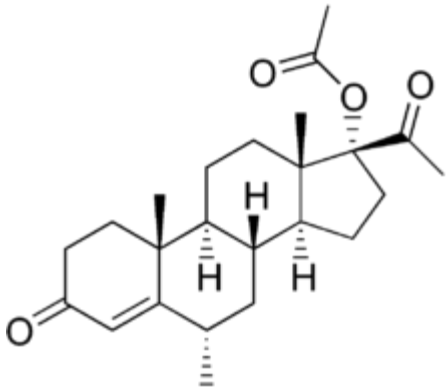
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

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

Chemical structure

MPA is 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.pfizer.com.au.

9. DATE OF FIRST APPROVAL

31 May 1993.

10. DATE OF REVISION

TBC.

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
All	Reformat to SmPC format
2; 3; 4; 5; & 6	Editorial
7	CAS number added
8	Sponsor details updated

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s22

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).[1]

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.[1] An evaluation of BMD may also be appropriate in some patients who use DEPO-PROVERA long-term for oncology indications.[2]

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.

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.[3]

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.[1] 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.[1] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[1] 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.[1]

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.[2]

An evaluation of BMD may be appropriate in some patients who use DEPO-PROVERA long term. [2]

It is recommended that all patients have adequate calcium and Vitamin D intake.[4]

Cancer risks

Long-term case-controlled surveillance of DEPO-PROVERA use for contraception found slight or no increased overall risk of breast cancer[6] and no increased overall risk of ovarian,[6] liver,[7] or cervical cancer.[8] There was a prolonged effect of reducing the risk of endometrial[9] 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)[1] 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.[11] The risk of breast cancer[6] was comparable in similar groups of women who used either DEPO-PROVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[11] 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.[12,13]

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.[14]

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)[15,16] (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.[1]

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.[17] 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.[18,19,20]

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).[21,22] 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[23]

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)[15,16]

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 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 syringe.[#]

[#]This presentation is not currently available in Australia.

6.6 Special precautions for disposal

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

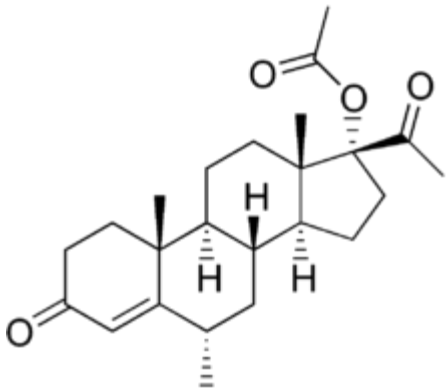
6.7 Physicochemical properties

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.pfizer.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, 5.1	Update to the post-treatment time to baseline BMD recovery

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s22 [redacted]

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

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium

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

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), women should be assessed before starting treatment for contraception or endometriosis, for the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak BMD (see Section 4.4 Special warnings and precautions for use).[1]

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.[1] An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications.[2]

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

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

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

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

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

4.4 Special warnings and precautions for use

Physical examination

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

Thromboembolic disorders

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

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of

women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.[3]

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

Bone mineral density changes

Contraception and endometriosis

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

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

In adolescent females, the decrease in BMD appears to fully reversible after DEPO-RALOVERA is discontinued and ovarian estrogen production increases.[1] Full recovery took 1.2 years at the lumbar spine, 4.6 years for total hip and 4.6 years at the femoral neck after therapy was discontinued. Longer duration of treatment and smoking were associated with slower recovery (see Section 5.1 Pharmacodynamic properties - Clinical trials - BMD changes in adolescent females (12 to 18 years)).)). In contrast, unmatched, untreated subjects showed mean BMD increases at 240 weeks of 6.4 %, 1.7 % and 1.9 % for lumbar spine, total hip and femoral neck, respectively.

DEPO-RALOVERA should only be used as a long-term (e.g., longer than 2 years) contraceptive method or treatment for endometriosis if other contraceptive methods or endometriotic treatments are inadequate. BMD should be evaluated DEPO-RALOVERA is used long term.[1] In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.[1] Since loss of BMD may occur in pre-menopausal women who use DEPO-RALOVERA long-term (greater than 2 years), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.[1]

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

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

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

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

However, two clinical studies of adult women of childbearing potential and of adolescent females given DEPO-RALOVERA 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Section 5.1 Pharmacodynamic properties - Clinical trials). Decreases in serum estrogen due to DEPO-RALOVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.[2]

An evaluation of BMD may be appropriate in some patients who use DEPO-RALOVERA long term. [2]

It is recommended that all patients have adequate calcium and Vitamin D intake.[4]

Cancer risks

Long-term case-controlled surveillance of DEPO-RALOVERA use for contraception found slight or no increased overall risk of breast cancer[5] and no increased overall risk of ovarian,[6] liver,[7] or cervical cancer.[8] There was a prolonged effect of reducing the risk of endometrial[9] cancer in the population of users, with a relative risk (RR) of 0.21 (95% Confidence Interval [CI] of 0.06-0.79). This protective effect lasts for at least 8 years after the cessation of DEPO-RALOVERA use.

The overall RR of breast cancer associated with the use of DEPO-RALOVERA appears to be 1.2 (95% CI 0.96-1.52). However, an increased RR of 2.19 (95% CI 1.23-3.89)[1] has been associated with use of DEPO-RALOVERA in women whose first exposure to the drug was within the previous 4 years and were under 35 years of age. The RR increases in women aged between 25 and 34 years of age (RR of 2 (95% CI 1.0-3.8) and rises to 4.6 (95% CI 1.4-15.1)) in women aged less than 25 years with more than 2 years exposure to DEPO-RALOVERA.[10] The risk of breast cancer[5] was comparable in similar groups of women who used either DEPO-RALOVERA or an oral contraceptive.

The Australian Institute of Health & Welfare[11] report, between 1983 to 1985, an average incidence rate for breast cancer in Australian women, aged 30 to 34 years, of 20.97/100,000. A RR of 2.19, thus, increases the possible risk from 20.97 to 45.92 cases per 100,000 women. The attributable risk, therefore, is 24.95 per 100,000 women per year.

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[12,13]

A significant increase in polysyndactyly and chromosomal anomalies was observed among infants of DEPO-RALOVERA users, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DEPO-RALOVERA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[14]

Ectopic pregnancy

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

Sexually transmitted infections

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

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

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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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

Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

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

General

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

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

DEPO-RALOVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years)[15] (see Section 5.1 Pharmacodynamic properties - Clinical trials). Other than concerns about loss of BMD, the safety and effectiveness of DEPO-RALOVERA are expected to be the same for postmenarcheal adolescent and adult females.

Effects on laboratory tests

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

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

4.5 Interactions with other medicines and other forms of interactions

Aminoglutethimide administered concomitantly with DEPO-RALOVERA may significantly decrease the serum concentration of MPA.[16] DEPO-RALOVERA users should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions – Return of fertility

Use in pregnancy – Pregnancy Category D

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

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

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

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

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

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

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

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

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

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

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

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

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

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

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

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

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

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

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

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

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

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

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

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

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-RALOVERA.[17,18,19]

There have been post-marketing reports of lipodystrophy acquired.

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

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

Reporting suspected adverse effects

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

4.9 Overdose

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

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

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with

DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method).[20.21] The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Clinical trials

Bone mineral density changes in adult women[22]

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

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

BMD changes in adolescent females (12 to 18 years)[15, 23]

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

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

5.2 Pharmacokinetic properties

Absorption

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

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

Metabolism

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

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

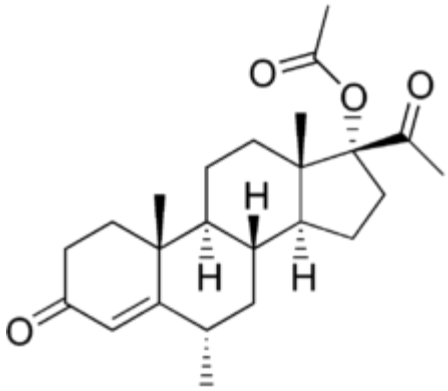
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

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

Chemical structure

MPA is 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.pfizer.com.au.

9. DATE OF FIRST APPROVAL

31 May 1993.

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4, 5.1	Update to post-treatment time to baseline BMD recovery

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Document 16

s22

DEPO-PROVERA®
medroxyprogesterone acetate 150 mg/1 mL
Suspension for Injection
s22
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
DEPO-PROVERA®
medroxyprogesterone acetate 150 mg/1 mL
Suspension for Injection
FOR INTRAMUSCULAR USE
1 x 1 mL disposable pre-filled syringe
AUST R 401610
Lot:
Exp:
Carton should contain colored overprint area
Pfizer Australia Pty Ltd
Sydney NSW
Pfizer New Zealand Limited
Auckland, New Zealand
In Australia, Consumer Medicine Information is available from your pharmacist, www.pfizermedinfo.com.au or ph. 1800 675 229.
In New Zealand, go to www.pfizermedinfo.co.nz or ph. 0800 736 363.
® Registered Trademark
0 000000 000000
Each 1 mL syringe contains:
medroxyprogesterone acetate 150 mg,
methyl hydroxybenzoate 1.35 mg,
propyl hydroxybenzoate 0.15 mg,
macrogol-3350 28.5 mg,
polysorbate-80 2.4 mg,
sodium chloride 8.6 mg,
water for injections to 1 mL.
Contains hydroxybenzoates.
Store below 30°C.
Do NOT refrigerate or freeze.
Directions for use:
Shake well before use.
Use in one patient on one occasion only and discard any residue.
Please refer to enclosed leaflet.
PAA201055
GLUE AREA
DEPO-PROVERA®
medroxyprogesterone acetate
150 mg/1 mL
Suspension for Injection
PAA 201055

s22

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.

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.

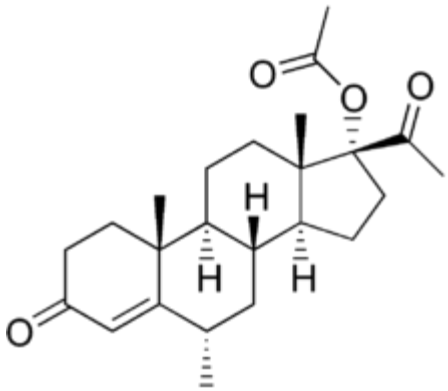
6.7 Physicochemical properties

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.pfizer.com.au

9. DATE OF FIRST APPROVAL

2 August 1991.

10. DATE OF REVISION

TBA

® 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.

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

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

DEPO-RALOVERA contains methyl hydroxybenzoate, propyl hydroxybenzoate and sodium

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

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

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

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

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

Breast carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

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

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

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

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

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

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

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

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

4.4 Special warnings and precautions for use

Physical examination

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

Thromboembolic disorders

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

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

As women continued to use DEPO-RALOVERA, fewer experienced intermenstrual bleeding and more experience amenorrhoea. By month 12, amenorrhoea was reported by 57% of

women, and by month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

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

Bone mineral density changes

Contraception and endometriosis

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

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

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

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

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

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

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

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

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

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

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

Cancer risks

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

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

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

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

Accidental pregnancies

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

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

Ectopic pregnancy

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

Sexually transmitted infections

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

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

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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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

Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

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

General

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

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

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

Effects on laboratory tests

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

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

4.5 Interactions with other medicines and other forms of interactions

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

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy – Pregnancy Category D

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

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

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

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

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

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

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

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

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

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

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

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

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

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

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

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

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

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

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

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

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

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

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

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

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-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

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

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

Reporting suspected adverse effects

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

4.9 Overdose

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

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

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with

DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

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

Clinical trials

Bone mineral density changes in adult women

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

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

BMD changes in adolescent females (12 to 18 years)

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

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

5.2 Pharmacokinetic properties

Absorption

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

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

Metabolism

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

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

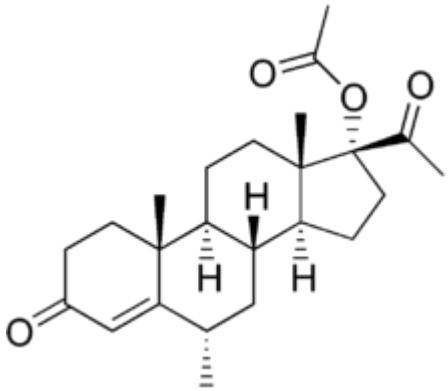
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

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

Chemical structure

MPA is 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.pfizer.com.au.

9. DATE OF FIRST APPROVAL

31 May 1993.

10. DATE OF REVISION

TBA

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes
6.4	Updated special precautions for storage, ‘Do not refrigerate or freeze’.

DEPO-PROVERA®
medroxyprogesterone acetate 150 mg/1 mL
Suspension for Injection
Contains:
1 x 1mL disposable pre-filled syringe
1 x sterile needle
s22
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
DEPO-PROVERA®
medroxyprogesterone acetate 150 mg/1 mL
Suspension for Injection
FOR INTRAMUSCULAR USE
1 x 1 mL disposable pre-filled syringe
AUST R 401610
Lot:
Exp:
Carton should contain colored overprint area
Pfizer Australia Pty Ltd
Sydney NSW
In Australia, Consumer Medicine Information is available from your pharmacist,
www.pfizermedinfo.com.au or ph. 1800 675 229.
Packed at Pfizer Manufacturing Belgium, Puurs-Sint-Amands, Belgium
® Registered Trademark
5 415062 109168
Pfizer
DEPO-PROVERA®
medroxyprogesterone acetate
150 mg/1 mL
Suspension for Injection
Each 1 mL syringe contains:
medroxyprogesterone acetate 150 mg,
methyl hydroxybenzoate 1.35 mg,
propyl hydroxybenzoate 0.15 mg,
macrogol-3350 28.5 mg,
polysorbate-80 2.4 mg,
sodium chloride 8.6 mg,
water for injections to 1 mL.
Contains hydroxybenzoates.
Store below 30°C.
Do NOT refrigerate or freeze.
Directions for use:
Shake well before use.
Use in one patient on one occasion only and discard any residue.
Please refer to enclosed leaflet.
PAA201055
GLUE AREA
PAA 201055

s22

DEPO-PROVERA®
medroxyprogesterone acetate 150 mg/1 mL
Suspension for Injection
Contains:
1 x 1mL disposable pre-filled syringe
1 x sterile needle
s22
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
DEPO-PROVERA®
medroxyprogesterone acetate 150 mg/1 mL
Suspension for Injection
FOR INTRAMUSCULAR USE
1 x 1 mL disposable pre-filled syringe
AUST R 401610
Pfizer Australia Pty Ltd
Sydney NSW
In Australia, Consumer Medicine Information is available from your pharmacist,
www.pfizermedinfo.com.au or ph. 1800 675 229.
Packed at Pfizer Manufacturing Belgium, Puurs-Sint-Amands, Belgium
® Registered Trademark
5 415062 109168
OVERPRINT AREA
Lot:
Exp:
Market code area (if required)
DEPO-PROVERA®
medroxyprogesterone acetate
150 mg/1 mL
Suspension for Injection
Pfizer
Each 1 mL syringe contains:
medroxyprogesterone acetate 150 mg,
methyl hydroxybenzoate 1.35 mg,
propyl hydroxybenzoate 0.15 mg,
macrogol-3350 28.5 mg,
polysorbate-80 2.4 mg,
sodium chloride 8.6 mg,
water for injections to 1 mL.
Contains hydroxybenzoates.
Store below 30°C.
Do NOT refrigerate or freeze.
Directions for use:
Shake well before use.
Use in one patient on one occasion only and discard any residue.
Please refer to enclosed leaflet.
PAA214625
GLUE AREA
GLUE AREA
GLUE AREA

s22

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.

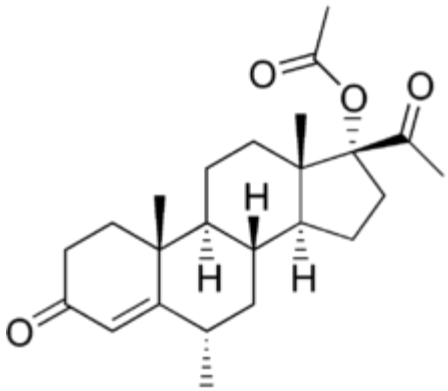
6.7 Physicochemical properties

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

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

1. NAME OF THE MEDICINE

medroxyprogesterone acetate (MPA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

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

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

3. PHARMACEUTICAL FORM

Injection, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

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

4.2 Dose and method of administration

Inoperable, recurrent, metastatic, endometrial & renal carcinoma

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

Breast carcinoma

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

Endometriosis

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

Contraception (ovulation suppression)

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

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

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

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

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

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

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

4.3 Contraindications

DEPO-RALOVERA is contraindicated in patients with:

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

4.4 Special warnings and precautions for use

Physical examination

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

Thromboembolic disorders

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

Meningioma

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

Ocular disorders

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

Bleeding irregularities

Most women receiving DEPO-RALOVERA for contraception experienced disruption of menstrual bleeding patterns. Altered bleeding patterns including irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigations should be instituted to rule out the possibility of organic pathology and appropriate treatment should be instituted when necessary.

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

women, and by Month 24, amenorrhoea was reported by 68% of women using DEPO-RALOVERA.

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

Bone mineral density changes

Contraception and endometriosis

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

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

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

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

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

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

See Section 5.1 Pharmacodynamic properties - Clinical trials.

Oncology

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

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

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

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

Cancer risks

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

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

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

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

Accidental pregnancies

Infants from accidental pregnancies that occur 1 to 2 months after injection of DEPO-RALOVERA may be at increased risk of low birth weight, which in turn may be associated

with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.

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

Ectopic pregnancy

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

Sexually transmitted infections

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

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

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

Anaphylactic and anaphylactoid reactions

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

Fluid retention

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

Breakthrough bleeding

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

Carbohydrate metabolism

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

CNS disorders and convulsions

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

Weight changes

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

Return of fertility

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

Liver function

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

Patient age

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

Pathology tests

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

IM administration

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

General

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

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

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

Effects on laboratory tests

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

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

4.5 Interactions with other medicines and other forms of interactions

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

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy – Pregnancy Category D

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

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

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

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

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

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

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

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

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

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

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

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

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

Endocrine disorders: Prolonged anovulation, Cushingoid syndrome.

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Depression, insomnia, nervousness.

Renal and urinary system disorders: Glycosuria.

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

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism.

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

Vascular disorders: Embolism and thrombosis, thrombophlebitis.

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

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

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

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

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

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

Blood and lymphatic system disorders: Blood dyscrasia, anaemia.

Cardiac disorders: Tachycardia, chest pain.

Gastrointestinal disorders: Gastrointestinal disorders, vomiting, rectal bleeding.

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

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-RALOVERA.

There have been post-marketing reports of lipodystrophy acquired.

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

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

Reporting suspected adverse effects

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

4.9 Overdose

No serious medical effects have been reported in association with overdosage of DEPO-RALOVERA injection suspension.

Oral doses up to 3 g per day have been well tolerated. Patients receiving pharmacological doses of MPA for treatments of neoplasms (400 mg/day or greater) may occasionally exhibit effects resembling those of glucocorticoid excess.

As with the management of any overdosage, the physician should carefully observe the patient for the potential side effects. Overdose treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Animal

MPA induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone and, when injected as a suspension, has a long duration of action. MPA induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. In selected animal tests it has some adrenocorticoid-like activity and in dogs increases serum growth hormone levels.

Human

DEPO-RALOVERA is a progestational agent with prolonged progestational effects when administered by intramuscular (IM) injection. When administered 3 monthly in recommended doses to women with adequate endogenous estrogen, it transforms proliferative into secretory endometrium. MPA inhibits gonadotrophin production, which in turn prevents follicular

maturation and ovulation. These actions produce the contraceptive effect. In 5 DEPO-RALOVERA clinical studies, the 3-month failure rate for the group of women treated with DEPO-RALOVERA was zero (no pregnancies reported to 0.7 by Life-Table method). The effectiveness of DEPO-RALOVERA is dependent on the woman returning every 3 months for re-injection.

Women with lower body weights conceive sooner than women with higher body weights after discontinuation of DEPO-RALOVERA.

Clinical trials

Bone mineral density changes in adult women

In a controlled, clinical study adult women using DEPO-RALOVERA (150 mg IM) for up to 5 years for contraception showed spine and hip mean bone mineral density (BMD) decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.9%, -4.1%, -4.9%, -4.9% and -5.4%after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-RALOVERA (150 mg IM), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. A longer duration of treatment was associated with a slower rate of BMD recovery. See Section 4.4 Special warnings and precautions for use.

BMD changes in adolescent females (12 to 18 years)

An open-label non-randomised clinical study of DEPO-RALOVERA (150 mg IM every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that DEPO-RALOVERA use was associated with a significant decline in BMD from baseline. Among subjects who received ≥ 4 injections/60-week period, the mean decrease in lumbar spine BMD was -2.1 % after 240 weeks; mean decreases for the total hip and femoral neck were -6.4 % and -5.4 %, respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche.

Based on mean changes, post-treatment follow-up showed that lumbar spine BMD recovered to baseline levels approximately 1.2 years after treatment was discontinued and hip and femoral neck BMD recovered to baseline levels approximately 4.6 years after treatment was discontinued (see Section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption

Parenteral MPA is a long acting progestational steroid. Its long duration of action results from its slow absorption from the injection site.

Following a single 150 mg IM dose of DEPO-RALOVERA, MPA levels increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL. The levels then decrease exponentially until they become undetectable (<100 pg/mL) between 120 and 200 days following the injection. Considerable interindividual variability in serum levels occurs after administration of standard doses of IM MPA.

Metabolism

MPA is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine, both as conjugated and free forms.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350

Sodium chloride

Polysorbate 80

Methyl hydroxybenzoate

Propyl hydroxybenzoate

Water for Injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

DEPO-RALOVERA 150 mg/mL injection suspension is supplied as 1 x 1 mL vials.

6.6 Special precautions for disposal

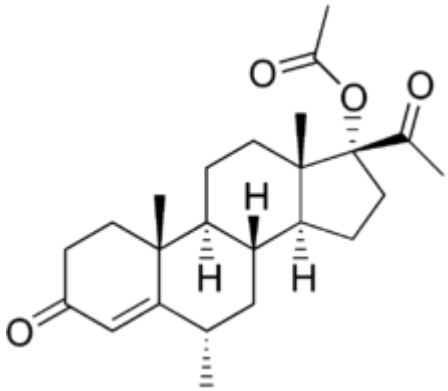
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

MPA is a progestogen and a derivative of progesterone. It is a white to off-white, odourless crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

Chemical structure

MPA is 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

31 May 1993

10. DATE OF REVISION

DD Month YYYY

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding meningioma Minor editorial changes
8	Update to sponsor website address

DEPO-PROVERA®

Document 21

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using DEPO-PROVERA?

DEPO-PROVERA contains the active ingredient medroxyprogesterone acetate. DEPO-PROVERA is used as a form of contraception, to treat endometriosis and certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus).

For more information, see Section 1. Why am I using DEPO-PROVERA? in the full CMI.

2. What should I know before I use DEPO-PROVERA?

Do not use if you have ever had an allergic reaction to medroxyprogesterone acetate or any of the ingredients listed at the end of the CMI.
Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant, plan to become pregnant or are breastfeeding.
For more information, see Section 2. What should I know before I use DEPO-PROVERA? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with DEPO-PROVERA and affect how it works.
A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How is DEPO-PROVERA given?

- DEPO-PROVERA is given as an injection into the muscle of your buttock. Your doctor or a trained nurse will give you the injection.
- The amount of DEPO-PROVERA and the number of injections that you receive will depend on the reason for the treatment.

More instructions can be found in Section 4. How is DEPO-PROVERA given? in the full CMI.

5. What should I know while using DEPO-PROVERA?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using DEPO-PROVERA. • Tell your doctor immediately if you have sudden partial or complete loss of vision or sudden onset of double vision or migraine while you are using DEPO-PROVERA. • Tell your doctor if you are pregnant or have become pregnant while using DEPO-PROVERA. • Tell your doctor if you are about to have any pathology tests (e.g. blood or urine tests).
Driving or using machines	• Do not drive or operate machinery until you know how DEPO-PROVERA affects you. DEPO-PROVERA may cause dizziness, sleepiness or affect vision in some people.
Looking after your medicine	• Keep DEPO-PROVERA in a cool dry place where the temperature stays below 30°C. Normally you should take DEPO-PROVERA straight from the pharmacy to your doctor. Do not leave it in a car. • Keep out of reach of children. • Follow the instructions in the carton on how to take care of your medicine properly.

For more information, see Section 5. What should I know while using DEPO-PROVERA? in the full CMI.

6. Are there any side effects?

There are a number of side effects associated with this medicine. See the full CMI for more details. The most common and serious side effects are: nausea, dizziness, headache, fatigue or sleepiness, trouble sleeping, hot flushes, changes in mood or mental state, changes to menstrual period or vaginal secretions, skin problems, excessive hair growth or loss, breast tenderness or secretions, weight changes, bloating or swelling, decreased libido, vision problems, allergic reactions, pressure or tightness in the chest, pain, discomfort or weakness in the back, legs, joints, pelvis, calves or abdomen, fainting, sudden migraine onset, hand tremors, seizures, paralysis or yellowing of the skin and/or eyes.
For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

DEPO-PROVERA®

Active ingredient(s): *medroxyprogesterone acetate*

Consumer Medicine Information (CMI)

This leaflet provides important information about using DEPO-PROVERA. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using DEPO-PROVERA.**

Where to find information in this leaflet:

1. Why am I using DEPO-PROVERA?
2. What should I know before I use DEPO-PROVERA?
3. What if I am taking other medicines?
4. How is DEPO-PROVERA given?
5. What should I know while using DEPO-PROVERA?
6. Are there any side effects?
7. Product details

1. Why am I using DEPO-PROVERA?

DEPO-PROVERA contains the active ingredient medroxyprogesterone acetate. DEPO-PROVERA is a progestogen, similar to the natural hormone progesterone. Your ovaries produce progesterone during the second half of your monthly cycle.

DEPO-PROVERA is used as a form of contraception, to treat endometriosis and also certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus).

Contraception

DEPO-PROVERA is an injectable form of contraception. Each injection protects you from pregnancy for 3 months.

DEPO-PROVERA works by inhibiting the hormones that are needed for the release of eggs from your ovaries.

Endometriosis

Endometriosis is a condition in which cells from the lining of the uterus (womb) grow in places outside the uterus.

During your period, these cells may grow and break down in the same way as those in the lining of the uterus. This causes pain and discomfort. DEPO-PROVERA helps to stop the growth of cells outside the uterus.

Cancer

DEPO-PROVERA is also used in the treatment of certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus). It works by inhibiting the growth of these types of cancer cells. DEPO-PROVERA is not a cure for cancer.

Your doctor may have prescribed DEPO-PROVERA for another purpose. Ask your doctor if you have any questions about why DEPO-PROVERA has been prescribed for you.

2. What should I know before I use DEPO-PROVERA?

Warnings

Do not use DEPO-PROVERA if:

1. you are allergic to medroxyprogesterone acetate, or any of the ingredients listed at the end of this leaflet.

Always check the ingredients to make sure you can use this medicine.

2. you have or have had any of the following medical conditions:

- swelling and redness along a vein (usually extremely tender when touched)
- a stroke or blood clots
- liver problems
- unusual or irregular vaginal bleeding that has not been diagnosed
- blood in your urine that has not been diagnosed
- any lumps or issues with your breast that have not been diagnosed, including any bleeding or discharge from your nipples.
- a missed miscarriage
- severe, uncontrolled, high blood pressure
- breast cancer, whether known or suspected (except when used for cancer treatment).

3. you are pregnant or suspect you may be pregnant.
4. it has passed the expiry date (EXP) printed on the pack or if the packaging is torn or shows signs of tampering.

Check with your doctor if you:

- have allergies to any medicines, foods, preservatives or dyes.
- have any other medical conditions, such as:
  - blood clots in your legs, lungs or anywhere else in your body
  - swollen red veins
  - stroke
  - liver problems
  - unusual or irregular vaginal bleeding or spotting
  - abnormal menstrual periods
  - breast cancer or a family history of breast cancer
  - any problems with your breasts
  - blood pressure problems
  - epilepsy
  - migraine
  - asthma
  - heart problems
  - kidney problems
  - diabetes
  - depression
  - bone disease, or a family history of bone disease, such as brittle bones (osteoporosis)

- vision problems
- fluid retention issues
- eating disorders (anorexia).

- take any medicines for any other condition.

  Some medicines may affect how well DEPO-PROVERA works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor will advise you.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

DEPO-PROVERA should not be used if you are pregnant or intend to become pregnant.

Check with your doctor if you are pregnant or intend to become pregnant.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

Physical examinations

Before prescribing DEPO-PROVERA for you, your doctor may conduct a physical examination which may include breast and pelvic examinations and/or a PAP smear.

Sexually transmitted infections (STIs)

- DEPO-PROVERA is intended to prevent pregnancy. It will not protect you from sexually transmitted diseases such as AIDS (HIV), Hepatitis B and C, genital herpes, genital warts, syphilis or gonorrhoea. Talk to your doctor about how to avoid these diseases.
- Using DEPO-PROVERA as directed will not expose you to STIs, as it is a sterile injection product.
- Practising safe sex (ie. using condoms) can lower the risk of STI transmission, including HIV, through sexual contact.

Breast cancer

- If you are under 35 years of age when you first start treatment with DEPO-PROVERA, you may have a slightly increased risk of developing breast cancer. This is similar to the risk with oral contraceptives ("the Pill"). If you have any concerns about this, please discuss them with your doctor.

Bone mineral density (BMD) changes

- The use of DEPO-PROVERA results in a decrease in the amount of calcium stored in your bones. This could increase your risk of developing brittle bones (osteoporosis), which can lead to bone breakages in later life. This affects women of all ages; however, it can be greater if you are under 18 years old. Your doctor will assess this risk before giving you DEPO-PROVERA and if you continue using DEPO-PROVERA for more than 2 years.
- The amount of calcium in your bones will start to increase again once you stop treatment with DEPO-PROVERA. The time to recovery depends on duration of use. Some women may only partially recover the amount of calcium in their bone. Talk to your doctor if you have any concerns over the risk of developing osteoporosis.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Medicines that may <u>reduce</u> the effect of DEPO-PROVERA include:

- aminoglutethine, a medicine used for the treatment of breast cancer.

Your doctor or pharmacist may have more information on medicines to be careful with or avoid while being treated with DEPO-PROVERA.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect DEPO-PROVERA.

4. How is DEPO-PROVERA given?

DEPO-PROVERA is given as an injection into the muscle of your buttock. Your doctor or a trained nurse will give you the injection.

The amount of DEPO-PROVERA and the number of injections that you receive will depend on the reason for the treatment.

The dose for contraception and for endometriosis is much lower than for cancer.

How much is given?

Contraception

- The recommended dose of DEPO-PROVERA for effective contraception is 150 mg every three months. The contraceptive protection of DEPO-PROVERA starts as soon as you have the first injection.
- It is very important that you make arrangements to return to your doctor every three months for your injections to ensure that pregnancy is prevented.
- If you are using DEPO-PROVERA as a contraceptive for the first time, your first injection should only be given during the first 5 days after the start of your normal monthly period.
- If you are using DEPO-PROVERA as a form of contraception after the birth of your baby and if you are not breastfeeding, the first injection should be given within 5 days after the baby was born.
- If you are breastfeeding, the first injection should be given 6 weeks after the baby was born and after your doctor has checked that you are not pregnant.
- If you are switching from another form of contraception, then DEPO-PROVERA should be given in a way that ensures you have continuous contraceptive cover. For example, patients switching from the oral contraceptive pill should have their first

DEPO-PROVERA injection within 7 days after taking the last active pill.
- If the time between your injections is greater than 14 weeks, your doctor will need to check that you are not pregnant before they give you another injection.

Endometriosis

- The usual dosage is either 50 mg weekly or 100 mg every two weeks.
- Treatment for endometriosis is usually for at least 6 months.

Breast Cancer

- The usual dosage for breast cancer is 500 mg every day for 4 weeks. After the first 4 weeks, DEPO-PROVERA is given as a weekly injection of 500 mg or 1000 mg.
- Your doctor will determine how much you should receive and how long you should continue to receive these injections.

Other types of cancer

- The initial dose range of DEPO-PROVERA is 600 mg to 1200 mg every week. This is followed by an injection of 450 mg to 600 mg every 1 to 4 weeks.
- Your doctor will determine how much you will receive and how long you should continue to receive the injections.

If you forget to use DEPO-PROVERA

DEPO-PROVERA should be given as determined by your doctor.

It is important to keep your appointments with the doctor who will determine your dosing schedule.

If too much DEPO-PROVERA is given

If you think that you or anyone else may have been treated with too much DEPO-PROVERA, you or the person may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using DEPO-PROVERA?

Things you should do

Tell all doctors, dentists, and pharmacists who are treating you that you have been treated with DEPO-PROVERA, particularly if you are about to have any pathology tests (e.g., blood or urine tests). DEPO-PROVERA may interfere with the results.

If you are about to be started on any new medicine, tell your doctor, dentist or pharmacist that you have been treated with DEPO-PROVERA.

Call your doctor straight away if you:

- become pregnant while using DEPO-PROVERA. The chance of falling pregnant while using DEPO-PROVERA as a contraceptive is low.
- if you have sudden partial or complete loss of vision or sudden onset of double vision or migraine while you are using DEPO-PROVERA, tell your doctor immediately.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how DEPO-PROVERA affects you.

DEPO-PROVERA may cause dizziness, sleepiness or affect vision in some people. Make sure you know how you react to DEPO-PROVERA before driving a car or operating machinery.

Drinking alcohol

Tell your doctor if you drink alcohol.

There is no information on how DEPO-PROVERA and alcohol may interact.

Looking after your medicine

- Keep DEPO-PROVERA in a cool dry place where the temperature stays below 30°C. Normally you should take DEPO-PROVERA straight from the pharmacy to your doctor. Do not leave it in a car.
- If for any reason you take your DEPO-PROVERA home, always ensure that it is stored in a place where children cannot reach it.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on window sills.

Do not use this medicine after the expiry date.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

Tell your doctor or pharmacist as soon as possible if you do not feel well during or after treatment with DEPO-PROVERA.

Most women using DEPO-PROVERA for contraception experience changes in their normal monthly period. This includes irregular or unpredictable bleeding or spotting or,

rarely, heavy or continuous bleeding. If abnormal bleeding continues or is severe, see your doctor immediately.

With continued use of DEPO-PROVERA, it is usual for vaginal bleeding to decrease. Your periods may stop completely.

When you stop treatment with DEPO-PROVERA, your periods will return. However, this may take up to 18 months. Most women find that it takes 12 to 18 months after their last injection to become pregnant. The length of time that you use DEPO-PROVERA does not affect the time it takes for you to become pregnant. If you do not wish to become pregnant after you stop using DEPO-PROVERA, you or your partner should use another form of contraception.

A reduction in the amount of calcium stored in your bones leading to brittle bones (osteoporosis) or fractures may occur. Tell your doctor if this worries you.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Side effects

Side effects	What to do
Changes to your mood or energy levels: • nervousness, confusion • increased heart rate • euphoria • loss of concentration • depression • fatigue, drowsiness or sleepiness • trouble sleeping **General feeling of being unwell:** • nausea, vomiting, diarrhoea or constipation • dizziness, headache • sweating • hot flushes • high fever **Changes to your hair, skin or eyes:** • hives, rash or itching • acne, darkening patches of skin on the cheeks • excessive hair growth or unusual hair loss or thinning • vision problems **Changes to your digestive or urinary system and/or metabolism:** • dry mouth, increased thirst • weight increases or decreases • changes in appetite • abdominal pain, bloating or discomfort • frequently urinating	**Speak to your doctor if you have any of these side effects and they worry you.**
Changes to your reproductive system: • breast tenderness or secretions • pain during sex • changes in vaginal secretions • irregular vaginal bleeding or spotting • lack of menstrual periods • decreased libido or the inability to climax • impotence (in men being treated for cancer) • pain and inflammation of the vagina **Pain or swelling in your body:** • abscess formation at the injection site • backache, leg cramps, muscle spasms • joint pain • swelling or puffiness, fluid retention	

Serious side effects

Serious side effects	What to do
Signs of an allergic reaction, such as: • rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing **Pain or discomfort in your body:** • pressure or tightness in the chest, back or jaw pain, difficulty breathing, or coughing up blood • weakness or numbness in your arms or legs • severe pain or swelling in your calf • sudden onset of migraine • severe abdominal pain • hand tremors, sweating, cramps in calves at night **Changes to your body, face or eyes:** • changes in metabolism resulting in the loss of body fat in certain areas of your body such as your face • yellowing of the skin and/or eyes **Other:** • seizures, paralysis • fainting	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Other side effects not listed here may occur in some people. These include side effects that can only be detected with a blood test.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What DEPO-PROVERA contains

Active ingredient (main ingredient)	medroxyprogesterone acetate
Other ingredients (inactive ingredients)	macrogol 3350 polysorbate 80 sodium chloride methyl hydroxybenzoate propyl hydroxybenzoate water for Injections

Do not use this medicine if you are allergic to any of these ingredients.

DEPO-PROVERA does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

What DEPO-PROVERA looks like

DEPO-PROVERA is a white cloudy liquid.

DEPO-PROVERA contains 150 mg of medroxyprogesterone acetate in 1 mL solution. DEPO-PROVERA is supplied as:

- Vial (AUST R 12300)
- Pre-filled Syringe (AUST R XXXXXX).

Not all presentations may be marketed.

Who distributes DEPO-PROVERA

Pfizer Australia Pty Ltd

Sydney NSW

Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

This leaflet was prepared in TBA.

DEPO-RALOVERA®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using DEPO-RALOVERA?

DEPO-RALOVERA contains the active ingredient medroxyprogesterone acetate. DEPO-RALOVERA is used as a form of contraception, to treat endometriosis and certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus).
For more information, see Section 1. Why am I using DEPO-RALOVERA? in the full CMI.

2. What should I know before I use DEPO-RALOVERA?

Do not use if you have ever had an allergic reaction to medroxyprogesterone acetate or any of the ingredients listed at the end of the CMI.
Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant, plan to become pregnant or are breastfeeding.
For more information, see Section 2. What should I know before I use DEPO-RALOVERA? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with DEPO-RALOVERA and affect how it works.
A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How is DEPO-RALOVERA given?

- DEPO-RALOVERA is given as an injection into the muscle of your buttock. Your doctor or a trained nurse will give you the injection.
- The amount of DEPO-RALOVERA and the number of injections that you receive will depend on the reason for the treatment.

More instructions can be found in Section 4. How is DEPO-RALOVERA given? in the full CMI.

5. What should I know while using DEPO-RALOVERA?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using DEPO-RALOVERA. • Tell your doctor immediately if you have sudden partial or complete loss of vision or sudden onset of double vision or migraine while you are using DEPO-RALOVERA. • Tell your doctor if you are pregnant or have become pregnant while using DEPO-RALOVERA. • Tell your doctor if you are about to have any pathology tests (e.g. blood or urine tests).
Driving or using machines	• Do not drive or operate machinery until you know how DEPO-RALOVERA affects you. DEPO-RALOVERA may cause dizziness, sleepiness or affect vision in some people.
Looking after your medicine	• Keep DEPO-RALOVERA in a cool dry place where the temperature stays below 30°C. Do not keep it in the refrigerator or freezer. Normally you should take DEPO-RALOVERA straight from the pharmacy to your doctor. Do not leave it in a car. • Keep out of reach of children. • Follow the instructions in the carton on how to take care of your medicine properly.

For more information, see Section 5. What should I know while using DEPO-RALOVERA? in the full CMI.

6. Are there any side effects?

There are a number of side effects associated with this medicine. See the full CMI for more details. The most common and serious side effects are: nausea, dizziness, headache, fatigue or sleepiness, trouble sleeping, hot flushes, changes in mood or mental state, changes to menstrual period or vaginal secretions, skin problems, excessive hair growth or loss, breast tenderness or secretions, weight changes, bloating or swelling, decreased libido, vision problems, allergic reactions, pressure or tightness in the chest, pain, discomfort or weakness in the back, legs, joints, pelvis, calves or abdomen, fainting, sudden migraine onset, hand tremors, seizures, paralysis or yellowing of the skin and/or eyes.
For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

DEPO-RALOVERA®

Active ingredient(s): *medroxyprogesterone acetate*

Consumer Medicine Information (CMI)

This leaflet provides important information about using DEPO-RALOVERA. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using DEPO-RALOVERA.**

Where to find information in this leaflet:

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2. What should I know before I use DEPO-RALOVERA?
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4. How is DEPO-RALOVERA given?
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1. Why am I using DEPO-RALOVERA?

DEPO-RALOVERA contains the active ingredient medroxyprogesterone acetate. DEPO-RALOVERA is a progestogen, similar to the natural hormone progesterone. Your ovaries produce progesterone during the second half of your monthly cycle.

DEPO-RALOVERA is used as a form of contraception, to treat endometriosis and also certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus).

Contraception

DEPO-RALOVERA is an injectable form of contraception. Each injection protects you from pregnancy for 3 months.

DEPO-RALOVERA works by inhibiting the hormones that are needed for the release of eggs from your ovaries.

Endometriosis

Endometriosis is a condition in which cells from the lining of the uterus (womb) grow in places outside the uterus.

During your period, these cells may grow and break down in the same way as those in the lining of the uterus. This causes pain and discomfort. DEPO-RALOVERA helps to stop the growth of cells outside the uterus.

Cancer

DEPO-RALOVERA is also used in the treatment of certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus). It works by inhibiting the growth of these types of cancer cells. DEPO-RALOVERA is not a cure for cancer.

Your doctor may have prescribed DEPO-RALOVERA for another purpose. Ask your doctor if you have any questions about why DEPO-RALOVERA has been prescribed for you.

2. What should I know before I use DEPO-RALOVERA?

Warnings

Do not use DEPO-RALOVERA if:

1. you are allergic to medroxyprogesterone acetate, or any of the ingredients listed at the end of this leaflet.

Always check the ingredients to make sure you can use this medicine.

2. you have or have had any of the following medical conditions:

- swelling and redness along a vein (usually extremely tender when touched)
- a stroke or blood clots
- liver problems
- unusual or irregular vaginal bleeding that has not been diagnosed
- blood in your urine that has not been diagnosed
- any lumps or issues with your breast that have not been diagnosed, including any bleeding or discharge from your nipples.
- a missed miscarriage
- severe, uncontrolled, high blood pressure
- breast cancer, whether known or suspected (except when used for cancer treatment).

3. you are pregnant or suspect you may be pregnant.
4. it has passed the expiry date (EXP) printed on the pack or if the packaging is torn or shows signs of tampering.

Check with your doctor if you:

- have allergies to any medicines, foods, preservatives or dyes.
- Have or have had any other medical conditions, such as:
    - blood clots in your legs, lungs or anywhere else in your body
    - swollen red veins
    - stroke
    - brain and/or spinal cord tumour or abnormal growths
    - liver problems
    - unusual or irregular vaginal bleeding or spotting
    - abnormal menstrual periods
    - breast cancer or a family history of breast cancer
    - any problems with your breasts
    - blood pressure problems
    - epilepsy
    - migraine
    - asthma
    - heart problems
    - kidney problems
    - diabetes

- depression
- bone disease, or a family history of bone disease, such as brittle bones (osteoporosis)
- vision problems
- fluid retention issues
- eating disorders (anorexia).

- take any medicines for any other condition.

  Some medicines may affect how well DEPO-RALOVERA works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor will advise you

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

DEPO-RALOVERA should not be used if you are pregnant or intend to become pregnant.

Check with your doctor if you are pregnant or intend to become pregnant.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

Physical examinations

Before prescribing DEPO-RALOVERA for you, your doctor may conduct a physical examination which may include breast and pelvic examinations and/or a PAP smear.

Sexually transmitted infections (STIs)

- DEPO-RALOVERA is intended to prevent pregnancy. It will not protect you from sexually transmitted diseases such as AIDS (HIV), Hepatitis B and C, genital herpes, genital warts, syphilis or gonorrhoea. Talk to your doctor about how to avoid these diseases.
- Using DEPO-RALOVERA as directed will not expose you to STIs, as it is a sterile injection product.
- Practising safe sex (ie. using condoms) can lower the risk of STI transmission, including HIV, through sexual contact.

Breast cancer

- If you are under 35 years of age when you first start treatment with DEPO-RALOVERA, you may have a slightly increased risk of developing breast cancer. This is similar to the risk with oral contraceptives ("the Pill"). If you have any concerns about this, please discuss them with your doctor.

Bone mineral density (BMD) changes

- The use of DEPO-RALOVERA results in a decrease in the amount of calcium stored in your bones. This could increase your risk of developing brittle bones (osteoporosis), which can lead to bone breakages in later life. This affects women of all ages; however, it can be greater if you are under 18 years old. Your doctor will assess this risk before giving you DEPO-RALOVERA and if you continue using DEPO-RALOVERA for more than 2 years.
- The amount of calcium in your bones will start to increase again once you stop treatment with DEPO-RALOVERA. The time to recovery depends on duration of use. Some women may only partially recover the amount of calcium in their bone. Talk to your doctor if you have any concerns over the risk of developing osteoporosis.

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Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Medicines that may <u>reduce</u> the effect of DEPO-RALOVERA include:

- aminoglutethine, a medicine used for the treatment of breast cancer.

Your doctor or pharmacist may have more information on medicines to be careful with or avoid while being treated with DEPO-RALOVERA.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect DEPO-RALOVERA.

4. How is DEPO-RALOVERA given?

DEPO-RALOVERA is given as an injection into the muscle of your buttock. Your doctor or a trained nurse will give you the injection.

The amount of DEPO-RALOVERA and the number of injections that you receive will depend on the reason for the treatment.

The dose for contraception and for endometriosis is much lower than for cancer.

How much is given?

Contraception

- The recommended dose of DEPO-RALOVERA for effective contraception is 150 mg every three months. The contraceptive protection of DEPO-RALOVERA starts as soon as you have the first injection.
- It is very important that you make arrangements to return to your doctor every three months for your injections to ensure that pregnancy is prevented.
- If you are using DEPO-RALOVERA as a contraceptive for the first time, your first injection should only be given during the first 5 days after the start of your normal monthly period.
- If you are using DEPO-RALOVERA as a form of contraception after the birth of your baby and if you are not breastfeeding, the first injection should be given within 5 days after the baby was born.
- If you are breastfeeding, the first injection should be given 6 weeks after the baby was born and after your doctor has checked that you are not pregnant.
- If you are switching from another form of contraception, then DEPO-RALOVERA should be given in a way that ensures you have continuous

contraceptive cover. For example, patients switching from the oral contraceptive pill should have their first DEPO-RALOVERA injection within 7 days after taking the last active pill.
- If the time between your injections is greater than 14 weeks, your doctor will need to check that you are not pregnant before they give you another injection.

Endometriosis

- The usual dosage is either 50 mg weekly or 100 mg every two weeks.
- Treatment for endometriosis is usually for at least 6 months.

Breast Cancer

- The usual dosage for breast cancer is 500 mg every day for 4 weeks. After the first 4 weeks, DEPO-RALOVERA is given as a weekly injection of 500 mg or 1000 mg.
- Your doctor will determine how much you should receive and how long you should continue to receive these injections.

Other types of cancer

- The initial dose range of DEPO-RALOVERA is 600 mg to 1200 mg every week. This is followed by an injection of 450 mg to 600 mg every 1 to 4 weeks.
- Your doctor will determine how much you will receive and how long you should continue to receive the injections.

If you forget to use DEPO-RALOVERA

DEPO-RALOVERA should be given as determined by your doctor.

It is important to keep your appointments with the doctor who will determine your dosing schedule.

If too much DEPO-RALOVERA is given

If you think that you or anyone else may have been treated with too much DEPO-RALOVERA, you or the person may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using DEPO-RALOVERA?

Things you should do

Tell all doctors, dentists, and pharmacists who are treating you that you have been treated with DEPO-RALOVERA, particularly if you are about to have any pathology tests (e.g., blood or urine tests). DEPO-RALOVERA may interfere with the results.

If you are about to be started on any new medicine, tell your doctor, dentist or pharmacist that you have been treated with DEPO-RALOVERA.

Call your doctor straight away if you:

- become pregnant while using DEPO-RALOVERA. The chance of falling pregnant while using DEPO-RALOVERA as a contraceptive is low.
- if you have sudden partial or complete loss of vision or sudden onset of double vision or migraine while you are using DEPO-RALOVERA, tell your doctor immediately.

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Be careful before you drive or use any machines or tools until you know how DEPO-RALOVERA affects you.

DEPO-RALOVERA may cause dizziness, sleepiness or affect vision in some people. Make sure you know how you react to DEPO-RALOVERA before driving a car or operating machinery.

Drinking alcohol

Tell your doctor if you drink alcohol.

There is no information on how DEPO-RALOVERA and alcohol may interact.

Looking after your medicine

- Keep DEPO-RALOVERA in a cool dry place where the temperature stays below 30°C. Do not keep it in the refrigerator or freezer. Normally you should take DEPO-RALOVERA straight from the pharmacy to your doctor. Do not leave it in a car.
- If for any reason you take your DEPO-RALOVERA home, always ensure that it is stored in a place where children cannot reach it.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on window sills.

Do not use this medicine after the expiry date.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

Tell your doctor or pharmacist as soon as possible if you do not feel well during or after treatment with DEPO-RALOVERA.

Most women using DEPO-RALOVERA for contraception experience changes in their normal monthly period. This includes irregular or unpredictable bleeding or spotting or,

rarely, heavy or continuous bleeding. If abnormal bleeding continues or is severe, see your doctor immediately.

With continued use of DEPO-RALOVERA, it is usual for vaginal bleeding to decrease. Your periods may stop completely.

When you stop treatment with DEPO-RALOVERA, your periods will return. However, this may take up to 18 months. Most women find that it takes 12 to 18 months after their last injection to become pregnant. The length of time that you use DEPO-RALOVERA does not affect the time it takes for you to become pregnant. If you do not wish to become pregnant after you stop using DEPO-RALOVERA, you or your partner should use another form of contraception.

A reduction in the amount of calcium stored in your bones leading to brittle bones (osteoporosis) or fractures may occur. Tell your doctor if this worries you.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Side effects

Side effects	What to do
Changes to your mood or energy levels: • nervousness, confusion • increased heart rate • euphoria • loss of concentration • depression • fatigue, drowsiness or sleepiness • trouble sleeping **General feeling of being unwell:** • nausea, vomiting, diarrhoea or constipation • dizziness, headache • sweating • hot flushes • high fever **Changes to your hair, skin or eyes:** • hives, rash or itching • acne, darkening patches of skin on the cheeks • excessive hair growth or unusual hair loss or thinning • vision problems **Changes to your digestive or urinary system and/or metabolism:** • dry mouth, increased thirst • weight increases or decreases • changes in appetite • abdominal pain, bloating or discomfort • frequently urinating	**Speak to your doctor if you have any of these side effects and they worry you.**
Changes to your reproductive system: • breast tenderness or secretions • pain during sex • changes in vaginal secretions • irregular vaginal bleeding or spotting • lack of menstrual periods • decreased libido or the inability to climax • impotence (in men being treated for cancer) • pain and inflammation of the vagina **Pain or swelling in your body:** • abscess formation at the injection site • backache, leg cramps, muscle spasms • joint pain • swelling or puffiness, fluid retention	

Serious side effects

Serious side effects	What to do
Signs of an allergic reaction, such as: • rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing **Pain or discomfort in your body:** • pressure or tightness in the chest, back or jaw pain, difficulty breathing, or coughing up blood • weakness or numbness in your arms or legs • severe pain or swelling in your calf • sudden onset of migraine • severe abdominal pain • hand tremors, sweating, cramps in calves at night **Changes to your body, face or eyes:** • changes in metabolism resulting in the loss of body fat in certain areas of your body such as your face • yellowing of the skin and/or eyes **Other:** • seizures, paralysis • fainting • memory loss	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Serious side effects	What to do
• hearing loss	

Other side effects not listed here may occur in some people. These include side effects that can only be detected with a blood test.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What DEPO-RALOVERA contains

Active ingredient (main ingredient)	medroxyprogesterone acetate
Other ingredients (inactive ingredients)	macrogol 3350 polysorbate 80 sodium chloride methyl hydroxybenzoate propyl hydroxybenzoate water for Injections

Do not use this medicine if you are allergic to any of these ingredients.

DEPO-RALOVERA does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

What DEPO-RALOVERA looks like

DEPO-RALOVERA is a white cloudy liquid. DEPO-RALOVERA contains 150 mg of medroxyprogesterone acetate in 1 mL solution. DEPO-RALOVERA is supplied as a vial (AUST R 44464).

Who distributes DEPO-RALOVERA

Pfizer Australia Pty Ltd

Sydney NSW

Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

This leaflet was prepared in March 2024.

DEPO-PROVERA®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using DEPO-PROVERA?

DEPO-PROVERA contains the active ingredient medroxyprogesterone acetate. DEPO-PROVERA is used as a form of contraception, to treat endometriosis and certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus).

For more information, see Section 1. Why am I using DEPO-PROVERA? in the full CMI.

2. What should I know before I use DEPO-PROVERA?

Do not use if you have ever had an allergic reaction to medroxyprogesterone acetate or any of the ingredients listed at the end of the CMI.
Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant, plan to become pregnant or are breastfeeding.
For more information, see Section 2. What should I know before I use DEPO-PROVERA? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with DEPO-PROVERA and affect how it works.
A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How is DEPO-PROVERA given?

- DEPO-PROVERA is given as an injection into the muscle of your buttock. Your doctor or a trained nurse will give you the injection.
- The amount of DEPO-PROVERA and the number of injections that you receive will depend on the reason for the treatment.

More instructions can be found in Section 4. How is DEPO-PROVERA given? in the full CMI.

5. What should I know while using DEPO-PROVERA?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using DEPO-PROVERA. • Tell your doctor immediately if you have sudden partial or complete loss of vision or sudden onset of double vision or migraine while you are using DEPO-PROVERA. • Tell your doctor if you are pregnant or have become pregnant while using DEPO-PROVERA. • Tell your doctor if you are about to have any pathology tests (e.g. blood or urine tests).
Driving or using machines	• Do not drive or operate machinery until you know how DEPO-PROVERA affects you. DEPO-PROVERA may cause dizziness, sleepiness or affect vision in some people.
Looking after your medicine	• Keep DEPO-PROVERA in a cool dry place where the temperature stays below 30°C. Do not keep it in the refrigerator or freezer. Normally you should take DEPO-PROVERA straight from the pharmacy to your doctor. Do not leave it in a car. • Keep out of reach of children. • Follow the instructions in the carton on how to take care of your medicine properly.

For more information, see Section 5. What should I know while using DEPO-PROVERA? in the full CMI.

6. Are there any side effects?

There are a number of side effects associated with this medicine. See the full CMI for more details. The most common and serious side effects are: nausea, dizziness, headache, fatigue or sleepiness, trouble sleeping, hot flushes, changes in mood or mental state, changes to menstrual period or vaginal secretions, skin problems, excessive hair growth or loss, breast tenderness or secretions, weight changes, bloating or swelling, decreased libido, vision problems, allergic reactions, pressure or tightness in the chest, pain, discomfort or weakness in the back, legs, joints, pelvis, calves or abdomen, fainting, sudden migraine onset, hand tremors, seizures, paralysis or yellowing of the skin and/or eyes.
For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

DEPO-PROVERA®

Active ingredient(s): *medroxyprogesterone acetate*

Consumer Medicine Information (CMI)

This leaflet provides important information about using DEPO-PROVERA. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using DEPO-PROVERA.**

Where to find information in this leaflet:

1. Why am I using DEPO-PROVERA?
2. What should I know before I use DEPO-PROVERA?
3. What if I am taking other medicines?
4. How is DEPO-PROVERA given?
5. What should I know while using DEPO-PROVERA?
6. Are there any side effects?
7. Product details

1. Why am I using DEPO-PROVERA?

DEPO-PROVERA contains the active ingredient medroxyprogesterone acetate. DEPO-PROVERA is a progestogen, similar to the natural hormone progesterone. Your ovaries produce progesterone during the second half of your monthly cycle.

DEPO-PROVERA is used as a form of contraception, to treat endometriosis and also certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus).

Contraception

DEPO-PROVERA is an injectable form of contraception. Each injection protects you from pregnancy for 3 months.

DEPO-PROVERA works by inhibiting the hormones that are needed for the release of eggs from your ovaries.

Endometriosis

Endometriosis is a condition in which cells from the lining of the uterus (womb) grow in places outside the uterus.

During your period, these cells may grow and break down in the same way as those in the lining of the uterus. This causes pain and discomfort. DEPO-PROVERA helps to stop the growth of cells outside the uterus.

Cancer

DEPO-PROVERA is also used in the treatment of certain types of cancer including cancer of the breast, kidney and endometrium (lining of the uterus). It works by inhibiting the growth of these types of cancer cells. DEPO-PROVERA is not a cure for cancer.

Your doctor may have prescribed DEPO-PROVERA for another purpose. Ask your doctor if you have any questions about why DEPO-PROVERA has been prescribed for you.

2. What should I know before I use DEPO-PROVERA?

Warnings

Do not use DEPO-PROVERA if:

1. you are allergic to medroxyprogesterone acetate, or any of the ingredients listed at the end of this leaflet.

Always check the ingredients to make sure you can use this medicine.

2. you have or have had any of the following medical conditions:

- swelling and redness along a vein (usually extremely tender when touched)
- a stroke or blood clots
- liver problems
- unusual or irregular vaginal bleeding that has not been diagnosed
- blood in your urine that has not been diagnosed
- any lumps or issues with your breast that have not been diagnosed, including any bleeding or discharge from your nipples.
- a missed miscarriage
- severe, uncontrolled, high blood pressure
- breast cancer, whether known or suspected (except when used for cancer treatment).

3. you are pregnant or suspect you may be pregnant.
4. it has passed the expiry date (EXP) printed on the pack or if the packaging is torn or shows signs of tampering.

Check with your doctor if you:

- have allergies to any medicines, foods, preservatives or dyes.
- Have or have had any other medical conditions, such as:
    - blood clots in your legs, lungs or anywhere else in your body
    - swollen red veins
    - stroke
    - brain and/or spinal cord tumour or abnormal growths
    - liver problems
    - unusual or irregular vaginal bleeding or spotting
    - abnormal menstrual periods
    - breast cancer or a family history of breast cancer
    - any problems with your breasts
    - blood pressure problems
    - epilepsy
    - migraine
    - asthma
    - heart problems
    - kidney problems
    - diabetes

- depression
- bone disease, or a family history of bone disease, such as brittle bones (osteoporosis)
- vision problems
- fluid retention issues
- eating disorders (anorexia).

- take any medicines for any other condition.

  Some medicines may affect how well DEPO-PROVERA works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor will advise you.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

DEPO-PROVERA should not be used if you are pregnant or intend to become pregnant.

Check with your doctor if you are pregnant or intend to become pregnant.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

Physical examinations

Before prescribing DEPO-PROVERA for you, your doctor may conduct a physical examination which may include breast and pelvic examinations and/or a PAP smear.

Sexually transmitted infections (STIs)

- DEPO-PROVERA is intended to prevent pregnancy. It will not protect you from sexually transmitted diseases such as AIDS (HIV), Hepatitis B and C, genital herpes, genital warts, syphilis or gonorrhoea. Talk to your doctor about how to avoid these diseases.
- Using DEPO-PROVERA as directed will not expose you to STIs, as it is a sterile injection product.
- Practising safe sex (ie. using condoms) can lower the risk of STI transmission, including HIV, through sexual contact.

Breast cancer

- If you are under 35 years of age when you first start treatment with DEPO-PROVERA, you may have a slightly increased risk of developing breast cancer. This is similar to the risk with oral contraceptives ("the Pill"). If you have any concerns about this, please discuss them with your doctor.

Bone mineral density (BMD) changes

- The use of DEPO-PROVERA results in a decrease in the amount of calcium stored in your bones. This could increase your risk of developing brittle bones (osteoporosis), which can lead to bone breakages in later life. This affects women of all ages; however, it can be greater if you are under 18 years old. Your doctor will assess this risk before giving you DEPO-PROVERA and if you continue using DEPO-PROVERA for more than 2 years.
- The amount of calcium in your bones will start to increase again once you stop treatment with DEPO-PROVERA. The time to recovery depends on duration of use. Some women may only partially recover the amount of calcium in their bone. Talk to your doctor if you have any concerns over the risk of developing osteoporosis.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Medicines that may <u>reduce</u> the effect of DEPO-PROVERA include:

- aminoglutethine, a medicine used for the treatment of breast cancer.

Your doctor or pharmacist may have more information on medicines to be careful with or avoid while being treated with DEPO-PROVERA.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect DEPO-PROVERA.

4. How is DEPO-PROVERA given?

DEPO-PROVERA is given as an injection into the muscle of your buttock. Your doctor or a trained nurse will give you the injection.

The amount of DEPO-PROVERA and the number of injections that you receive will depend on the reason for the treatment.

The dose for contraception and for endometriosis is much lower than for cancer.

How much is given?

Contraception

- The recommended dose of DEPO-PROVERA for effective contraception is 150 mg every three months. The contraceptive protection of DEPO-PROVERA starts as soon as you have the first injection.
- It is very important that you make arrangements to return to your doctor every three months for your injections to ensure that pregnancy is prevented.
- If you are using DEPO-PROVERA as a contraceptive for the first time, your first injection should only be given during the first 5 days after the start of your normal monthly period.
- If you are using DEPO-PROVERA as a form of contraception after the birth of your baby and if you are not breastfeeding, the first injection should be given within 5 days after the baby was born.
- If you are breastfeeding, the first injection should be given 6 weeks after the baby was born and after your doctor has checked that you are not pregnant.
- If you are switching from another form of contraception, then DEPO-PROVERA should be given in a way that ensures you have continuous

contraceptive cover. For example, patients switching from the oral contraceptive pill should have their first DEPO-PROVERA injection within 7 days after taking the last active pill.
- If the time between your injections is greater than 14 weeks, your doctor will need to check that you are not pregnant before they give you another injection.

Endometriosis

- The usual dosage is either 50 mg weekly or 100 mg every two weeks.
- Treatment for endometriosis is usually for at least 6 months.

Breast Cancer

- The usual dosage for breast cancer is 500 mg every day for 4 weeks. After the first 4 weeks, DEPO-PROVERA is given as a weekly injection of 500 mg or 1000 mg.
- Your doctor will determine how much you should receive and how long you should continue to receive these injections.

Other types of cancer

- The initial dose range of DEPO-PROVERA is 600 mg to 1200 mg every week. This is followed by an injection of 450 mg to 600 mg every 1 to 4 weeks.
- Your doctor will determine how much you will receive and how long you should continue to receive the injections.

If you forget to use DEPO-PROVERA

DEPO-PROVERA should be given as determined by your doctor.

It is important to keep your appointments with the doctor who will determine your dosing schedule.

If too much DEPO-PROVERA is given

If you think that you or anyone else may have been treated with too much DEPO-PROVERA, you or the person may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using DEPO-PROVERA?

Things you should do

Tell all doctors, dentists, and pharmacists who are treating you that you have been treated with DEPO-PROVERA, particularly if you are about to have any pathology tests (e.g., blood or urine tests). DEPO-PROVERA may interfere with the results.

If you are about to be started on any new medicine, tell your doctor, dentist or pharmacist that you have been treated with DEPO-PROVERA.

Call your doctor straight away if you:

- become pregnant while using DEPO-PROVERA. The chance of falling pregnant while using DEPO-PROVERA as a contraceptive is low.
- if you have sudden partial or complete loss of vision or sudden onset of double vision or migraine while you are using DEPO-PROVERA, tell your doctor immediately.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how DEPO-PROVERA affects you.

DEPO-PROVERA may cause dizziness, sleepiness or affect vision in some people. Make sure you know how you react to DEPO-PROVERA before driving a car or operating machinery.

Drinking alcohol

Tell your doctor if you drink alcohol.

There is no information on how DEPO-PROVERA and alcohol may interact.

Looking after your medicine

- Keep DEPO-PROVERA in a cool dry place where the temperature stays below 30°C. Do not keep it in the refrigerator or freezer. Normally you should take DEPO-PROVERA straight from the pharmacy to your doctor. Do not leave it in a car.
- If for any reason you take your DEPO-PROVERA home, always ensure that it is stored in a place where children cannot reach it.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on window sills.

Do not use this medicine after the expiry date.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

Tell your doctor or pharmacist as soon as possible if you do not feel well during or after treatment with DEPO-PROVERA.

Most women using DEPO-PROVERA for contraception experience changes in their normal monthly period. This includes irregular or unpredictable bleeding or spotting or,

rarely, heavy or continuous bleeding. If abnormal bleeding continues or is severe, see your doctor immediately.

With continued use of DEPO-PROVERA, it is usual for vaginal bleeding to decrease. Your periods may stop completely.

When you stop treatment with DEPO-PROVERA, your periods will return. However, this may take up to 18 months. Most women find that it takes 12 to 18 months after their last injection to become pregnant. The length of time that you use DEPO-PROVERA does not affect the time it takes for you to become pregnant. If you do not wish to become pregnant after you stop using DEPO-PROVERA, you or your partner should use another form of contraception.

A reduction in the amount of calcium stored in your bones leading to brittle bones (osteoporosis) or fractures may occur. Tell your doctor if this worries you.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Side effects

Side effects	What to do
Changes to your mood or energy levels: • nervousness, confusion • increased heart rate • euphoria • loss of concentration • depression • fatigue, drowsiness or sleepiness • trouble sleeping **General feeling of being unwell:** • nausea, vomiting, diarrhoea or constipation • dizziness, headache • sweating • hot flushes • high fever **Changes to your hair, skin or eyes:** • hives, rash or itching • acne, darkening patches of skin on the cheeks • excessive hair growth or unusual hair loss or thinning • vision problems **Changes to your digestive or urinary system and/or metabolism:** • dry mouth, increased thirst • weight increases or decreases • changes in appetite • abdominal pain, bloating or discomfort • frequently urinating	**Speak to your doctor if you have any of these side effects and they worry you.**
Changes to your reproductive system: • breast tenderness or secretions • pain during sex • changes in vaginal secretions • irregular vaginal bleeding or spotting • lack of menstrual periods • decreased libido or the inability to climax • impotence (in men being treated for cancer) • pain and inflammation of the vagina **Pain or swelling in your body:** • abscess formation at the injection site • backache, leg cramps, muscle spasms • joint pain • swelling or puffiness, fluid retention	

Serious side effects

Serious side effects	What to do
Signs of an allergic reaction, such as: • rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing **Pain or discomfort in your body:** • pressure or tightness in the chest, back or jaw pain, difficulty breathing, or coughing up blood • weakness or numbness in your arms or legs • severe pain or swelling in your calf • sudden onset of migraine • severe abdominal pain • hand tremors, sweating, cramps in calves at night **Changes to your body, face or eyes:** • changes in metabolism resulting in the loss of body fat in certain areas of your body such as your face • yellowing of the skin and/or eyes **Other:** • seizures, paralysis • fainting • memory loss	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Serious side effects	What to do
• hearing loss	

Other side effects not listed here may occur in some people. These include side effects that can only be detected with a blood test.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What DEPO-PROVERA contains

Active ingredient (main ingredient)	medroxyprogesterone acetate
Other ingredients (inactive ingredients)	macrogol 3350 polysorbate 80 sodium chloride methyl hydroxybenzoate propyl hydroxybenzoate water for Injections

Do not use this medicine if you are allergic to any of these ingredients.

DEPO-PROVERA does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

What DEPO-PROVERA looks like

DEPO-PROVERA is a white cloudy liquid.

DEPO-PROVERA contains 150 mg of medroxyprogesterone acetate in 1 mL solution. DEPO-PROVERA is supplied as:

- Vial (AUST R 12300)
- Pre-filled Syringe (AUST R 401610).

Not all presentations may be marketed.

Who distributes DEPO-PROVERA

Pfizer Australia Pty Ltd

Sydney NSW

Toll Free Number: 1800 675 229

www.pfizermedicalinformation.com.au

This leaflet was prepared in March 2024.