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:

![Structural formula of medroxyprogesterone acetate](image)

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.
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
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)\textsuperscript{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).\textsuperscript{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
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. A study to assess the reversibility of loss of BMD in adolescent females is ongoing.

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

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.

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.

5. **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 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) 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. 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 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.

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.

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.
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 adrenocorticotropic 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 adrenocorticotropic 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. 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.
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.
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)
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)\textsuperscript{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.\textsuperscript{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
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 dyscrasias, 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, dysmenorrhea, 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\textsuperscript{20,21,22}.

**DOSAGE AND ADMINISTRATION**

<table>
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<tr>
<th>Indications</th>
<th>Dosage</th>
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<tr>
<td>Inoperable, recurrent, metastatic, endometrial &amp; renal carcinoma</td>
<td>Initially, 600-1200 mg weekly followed by 450-600 mg every 1-4 weeks for maintenance.</td>
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<tr>
<td>Breast Carcinoma</td>
<td>IM injection 500 mg daily for 4 weeks then 500 mg to 1000 mg at weekly intervals for maintenance.</td>
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<tr>
<td>Endometriosis</td>
<td>50 mg weekly or 100 mg every two weeks by intramuscular injection for at least six months.</td>
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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.  |

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\textsuperscript{4}. An evaluation of BMD may also be appropriate in some patients who use DEPO-RALOVERA long-term for oncology indications\textsuperscript{13}.

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 intramuscular 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:

- 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,

**REFERENCES**

(Available upon request from Pfizer Australia Pty Ltd)

4. Wolter KD. Clinical Overview to Support Bone Mineral Density Revisions dated Sep04 Pfizer Inc.


**SPONSOR**

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

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*Date of most recent amendment:* 25 August 2011

*Please note changes in Product Information*

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