PRODUCT INFORMATION
RALOVERA®
(Medroxyprogesterone acetate tablets)

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

![Structural formula of Medroxyprogesterone acetate]

PHARMACOLOGY

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

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

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

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

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

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

Animal Toxicology

Acute Toxicity: The oral LD$_{50}$ of medroxyprogesterone acetate was found to be >10,000 mg/kg in the mouse. The intraperitoneal LD$_{50}$ in the mouse was 6985 mg/kg.

Subacute and Chronic Toxicity: Medroxyprogesterone acetate administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

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

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

Carcinogenesis and Mutagenesis: Long-term toxicology studies in the monkey, dog and rat with parenteral medroxyprogesterone acetate have disclosed:

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

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

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

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

There are no studies on the bone mineral density (BMD) effects of RALOVERA. However, a clinical study of adult women of childbearing potential given medroxyprogesterone acetate (MPA) intra-muscular injection (IM) 150 mg every 3 months, for contraception, demonstrated an average decrease of 5.4% in lumbar spine BMD over 5 years, with at least partial recovery of this bone loss during the first two years after treatment is discontinued. A similar clinical study of MPA 150 mg IM injection every 3 months in adolescent females, for contraception, demonstrated similar decreases in BMD, which were also more pronounced during the first two years of treatment and which again were at least partially reversible when treatment was discontinued. Decreases in serum estrogen due to RALOVERA may result in a decrease in BMD in a premenopausal woman and may increase her risk for developing osteoporosis later in life.

See 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 contraindicated or has been unsuccessful.

3. Secondary Amenorrhoea proven not due to pregnancy: In amenorrhoea associated with a poorly developed proliferative endometrium, conventional oestrogen therapy may be employed in conjunction with medroxyprogesterone acetate.

4. Abnormal Uterine Bleeding; in the absence of organic pathology.

5. Adjunct to Oestrogen Therapy: Combination hormone replacement therapy should only be used in non-hysterectomised women (refer WARNINGS).

CONTRAINDICATIONS

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

2. Markedly impaired liver function.

3. Undiagnosed vaginal bleeding.


5. Undiagnosed breast pathology.

6. Missed abortion.
7. Known sensitivity to medroxyprogesterone acetate or to any of the excipients.

8. Known or suspected pregnancy: Category D

Animal studies have shown that high doses of progestogens can cause masculinization 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 fetuses. The risk of hypospadias may be approximately doubled with exposure to progesterones.

9. Severe uncontrolled hypertension.

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

**WARNINGS**

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

2. 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. 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 possesses adrenocorticoid activity.

4. The following laboratory tests may be affected by the use of 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) Sex-hormone-binding globulin
   (g) Plasma cortisol levels
   (h) Glucose tolerance test
   (i) Metyrapone test - the use of medroxyprogesterone acetate in oncology indications may cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of the adrenal cortex
to respond to adrenocorticotropic hormone should be demonstrated before metyrapone is administered.

5. Observational and randomised, prospective trials on the long-term effects of a combined oestrogen/progestin regimen in postmenopausal women have reported an increased risk of several disorders including cardiovascular diseases (e.g. coronary heart disease and stroke), breast cancer, and venous thromboembolism. Mortality can be increased in those who are diagnosed with incident breast cancers. The possible effect of hormone replacement therapy (HRT) on mammographic density and on the sensitivity and specificity of breast cancer screening should also be considered. Combination HRT should not be used in hysterectomised women because it is not needed to prevent endometrial changes in these women and it may increase the risk of breast cancer.

6. *Current use of oestrogen only or oestrogen plus progestin products in post-menopausal women for five or more years has been associated with an increased risk of ovarian cancer.

7. The benefits and risks of hormone replacement therapy (HRT) must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined oestrogen/progestin therapy in postmenopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in postmenopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without reexamining the patient.

**Decrease in Bone Mineral Density**

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

However, 2 clinical studies of adult women of childbearing potential and of adolescent females given medroxyprogesterone acetate 150 mg IM every 3 months, for contraception, demonstrated significant decreases in BMD (see Clinical Trials). Decreases in serum oestrogen due to 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 RALOVERA long term.

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

**Use in the Elderly**

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

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

PRECAUTIONS

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

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

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

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

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

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

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

If RALOVERA is used during pregnancy, or if the patient becomes pregnant while using RALOVERA, the patient should be apprised of the potential risk to the fetus.
NOTE: In perimenopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of hormone replacement therapy (HRT). An endometrial biopsy may be performed at the discretion of the attending physician.

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 acetate:

1. Allergy – hypersensitivity reactions (e.g. anaphylaxis, anaphylactoid-like reactions, angioedema).

2. Cardiovascular – cerebral and myocardial infarction, congestive heart failure, increased blood pressure, palpitations, retinal thrombosis, tachycardia, thromboembolic disease, thrombophlebitis, pulmonary embolism.

3. Central Nervous System – confusion, loss of concentration, euphoria, vision disorders, nervousness, insomnia, somnolence, fatigue, depression, dizziness, headache, and tremor. Some patients may complain of premenstrual-like depression while on RALOVERA.

4. Skin and Mucous Membranes - urticaria, pruritis, rash, acne, hirsutism, alopecia and sweating.

5. Genitourinary - irregular uterine bleeding, increase or decrease in uterine bleeding, spotting, prolonged anovulation and amenorrhoea.

6. Gastrointestinal/Hepatobiliary – nausea, vomiting, constipation, diarrhoea, dry mouth, disturbed liver function, jaundice.

7. Metabolic and Nutritional – adrenergic-like effects (e.g. fine-hand tremors, cramps in calves at night), corticoid-like effects (e.g. Cushingoid syndrome), decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria.

8. Breast – tenderness, galactorrhoea, mastodynia. The use of oestrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (refer WARNINGS).


10. Miscellaneous – changes in appetite, changes in libido, oedema/fluid retention, hyperpyrexia, weight change, malaise, hypercalcaemia.

11. 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.
DOSAGE AND ADMINISTRATION

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<thead>
<tr>
<th>Indications</th>
<th>Dosage of RALOVERA</th>
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<tbody>
<tr>
<td>Inoperable, recurrent metastatic, endometrial carcinoma</td>
<td>200-400 mg daily</td>
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<tr>
<td>Breast Carcinoma</td>
<td>500 mg daily until progression of disease</td>
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<tr>
<td>Renal Cell Carcinoma</td>
<td>200-400 mg daily</td>
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<tr>
<td>Endometriosis</td>
<td>Beginning the first day of the menstrual cycle 10 mg RALOVERA three times daily for 90 consecutive days.</td>
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<tr>
<td>Secondary Amenorrhoea not due to pregnancy.</td>
<td>2.5-10 mg daily for 5-10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for three consecutive cycles.</td>
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<td>Abnormal Uterine Bleeding in the absence of organic pathology</td>
<td>2.5-10 mg daily for 5-10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for three consecutive cycles.</td>
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<tr>
<td>Adjunct to Oestrogen Therapy #</td>
<td>10-20 mg per day for at least 10 days of each cycle. 5 mg per day continuously for 28 days of each cycle.</td>
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# Use of combined oestrogen/progestin therapy in postmenopausal women should be prescribed at the lowest effective doses and limited to the shortest duration consistent with treatment goals and risks for the individual women, and should be periodically evaluated. HRT in postmenopausal women is not generally appropriate for long term use and should not be prescribed for longer than 6 months without reexamining the patient.

OVERDOSAGE

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 overdose, 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.
PRESENTATION

RAOVERA Tablets containing medroxyprogesterone acetate.

2.5 mg tablets: (orange, circular, scored one side, marked U64 on the other) in blister packs of 28 and 56.

5 mg tablets:† (blue, circular, scored one side and marked 286 twice, marked U on the other) in blister packs of 56.

10 mg tablets:† (white, circular, scored marked UPJOHN 50) in blister packs of 30 and in bottles of 100.

100 mg tablets: (white, scored, marked U467) in blister packs of 100.

200 mg tablets: (white, scored, marked U320) in blister packs of 60.

250 mg tablets: (white, scored, marked U403) in blister packs of 60.

500 mg tablets: (white, capsule-shaped, marked UPJOHN 717 on one side only) in blister packs of 30.

† Strengths currently marketed.

REFERENCES

Available on request from Pfizer Australia Pty Ltd

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: 30 June 2009

* Please note changes in Product Information

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