

## PROVERA HD (High Dose)

Medroxyprogesterone Acetate PhEur 100mg and 200mg tablets

### Presentation

PROVERA 100mg tablets are white, round flat, scored one side, coded 'U467'.

PROVERA 200mg tablets are white round, biconvex, scored one side coded 'U320'.

### Uses

#### *Actions*

The anti-cancer activity of PROVERA at pharmacologic doses may be dependent upon its effect on the hypothalamic-pituitary-gonadal axis, oestrogen receptors and the metabolism of steroids at the tissue level.

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

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

The principal metabolite of medroxyprogesterone acetate that has been identified is a 6 alpha-methyl-6 beta, 17 alpha, 21-trihydroxy-4-pregnene-3, 20-dione-17-acetate, which is excreted in the urine.

#### *Clinical Trials*

##### BMD Changes

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

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 oestrogen due to PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

See Warnings and Precautions

## **Indications**

PROVERA is indicated as adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma and, in the treatment of hormonally-dependent, recurrent breast cancer in post-menopausal women.

## **Dosage and Administration**

### **ENDOMETRIAL AND RENAL CARCINOMA**

Doses of 100-600mg per day of PROVERA are recommended.

### **BREAST CANCER**

Doses of 400-1500mg per day are recommended. The patient should then be continued on therapy as long as she is responding to treatment.

NOTE: Response to hormonal therapy for endometrial, renal or breast cancer may not be evident until after 8 - 10 weeks of therapy. Rapid progression of disease at any time during therapy should terminate treatment with PROVERA.

PROVERA is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced, inoperable cases including those with recurrent or metastatic disease.

## **Contraindications**

- Known sensitivity to medroxyprogesterone acetate or to any component of the drug.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Severe liver dysfunction.

## **Warnings and Precautions**

- Unexpected vaginal bleeding during therapy with PROVERA should be investigated.
- PROVERA may cause some degree of fluid retention, therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.
- Patients with a history of treatment for clinical depression should be carefully monitored while receiving PROVERA therapy.
- Some patients receiving PROVERA may exhibit a decreased glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.
- The pathologist (laboratory) should be informed of the patient's use of PROVERA if endometrial or endocervical tissue is submitted for examination.
- The physician/laboratory should be informed that use of PROVERA may decrease the levels of the following endocrine biomarkers:
  - Plasma/urinary steroids (e.g., cortisol, oestrogen, pregnanediol, progesterone, testosterone)

- Plasma/urinary gonadotrophins (e.g., LH and FSH)
- Sex-hormone-binding-globulin.

Additionally, the use of PROVERA may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus the ability of adrenal cortex to respond to ACTH should be demonstrated before metyrapone is administered.

- Medication should not be readministered pending examination if there is a 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 not be readministered.
- Although PROVERA has not been causally associated with the induction of thrombotic or thromboembolic disorders, any patient with a history or who develops this kind of event while undergoing therapy with PROVERA should have their status and need for treatment carefully assessed before continuing therapy.
- PROVERA may produce cushingoid symptoms.
- Some patients receiving PROVERA may exhibit suppressed adrenal function. PROVERA may decrease ACTH and hydrocortisone blood levels.
- Decrease in Bone Mineral Density:

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

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 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.

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

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

### ***Pregnancy and Lactation***

PROVERA is contraindicated in women who are pregnant.

Some reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female foetuses.

Infants from unintentional pregnancies that occur 1 to 2 months after injection of medroxyprogesterone acetate injectable suspension may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because pregnancies while on medroxyprogesterone acetate are uncommon. There is no definitive information for the other formulations of medroxyprogesterone acetate.

If 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.

Medroxyprogesterone acetate and its metabolites are excreted in breast milk. There is no evidence to suggest that this presents any hazard to the nursing child.

## Adverse Effects

Body System	Event
Genitourinary	Abnormal uterine bleeding (irregular, increase, decrease), amenorrhoea, alterations of cervical secretions, cervical erosions, prolonged anovulation
Breast	Galactorrhea, mastodynia, tenderness
Central Nervous System	Confusion, depression, dizziness, euphoria, fatigue, headache, insomnia, loss of concentration, nervousness, somnolence, vision disorders
Gastrointestinal/Hepatobiliary	Constipation, diarrhoea, dry mouth, disturbed liver function, jaundice, nausea, vomiting
Metabolic & Nutritional	Adrenergic-like effects (e.g., fine-hand tremors, sweating, cramps in calves at night), corticoid-like effects (e.g., Cushingoid syndrome), decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria
Cardiovascular	Cerebral and myocardial infarction, congestive heart failure, increased blood pressure, palpitations, pulmonary embolism, retinal thrombosis, tachycardia, thromboembolic disorders, thrombophlebitis
Haematological	Elevation of white blood cells and platelet counts
Skin & Mucous Membranes	Acne, alopecia, hirsutism, pruritus, rash, urticaria
Allergy	Hypersensitivity reactions (e.g., anaphylaxis & anaphylactoid reactions, angioedema)
Miscellaneous	Changes in appetite, changes in libido, oedema/fluid retention, hypercalcemia, malaise, pyrexia, weight change

## Interactions

Aminoglutethimide administered concomitantly with high doses of medroxyprogesterone acetate may significantly depress the serum concentrations of medroxyprogesterone acetate. Users of high-dose PROVERA should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

## Overdosage

Nil.

## Pharmaceutical Precautions

Store at or below 25°C.

## **Medicine Classification**

Prescription medicine.

## **Package Quantities**

Blisters of 100, 100mg tablets.

Blisters of 30, 200mg tablets.

## **Further Information**

Nil.

## **Name and Address**

Pfizer New Zealand Ltd

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## **Date of Preparation**

12<sup>th</sup> November 2004

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