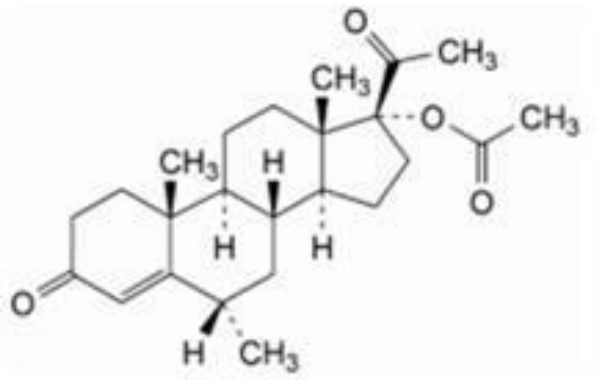
PRODUCT INFORMATION

PROVERA® (medroxyprogesterone acetate)

NAME OF THE MEDICINE

Medroxyprogesterone acetate (MPA) is 6α-methyl-3,20-dioxopregn-4-en-17α-yl acetate, and its 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.

PHARMACOLOGY

Pharmacodynamics

Animal

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

Human

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

Like progesterone, MPA 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

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

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

MPA 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 MPA 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: MPA 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.

MPA was administered orally to dogs and rats at 3 mg/kg/day, 10 mg/kg/day 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.

CLINICAL TRIALS

Bone mineral density changes

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

However, in a controlled, clinical study adult women using MPA intra-muscular (IM) injection, 150 mg every 3 months, 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 MPA IM injection 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.

An open-label non-randomised clinical study of MPA IM injection 150 mg every 12 weeks for up to 240 weeks (4.6 years) in adolescent females (12 to 18 years) for contraception also showed that MPA IM injection use was associated with a significant decline in BMD from baseline. Among subjects who received $\geq$ 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.

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).

Decreases in serum estrogen 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 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.

Secondary amenorrhoea proven not due to pregnancy

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with medroxyprogesterone acetate.

Abnormal uterine bleeding in the absence of organic pathology

Adjunct to estrogen therapy

Combination hormone replacement therapy should only be used in non-hysterectomised women (see PRECAUTIONS).

CONTRAINDICATIONS

PROVERA is contraindicated in patients with:

- thrombophlebitis, thrombotic or 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 to any of the excipients in the tablet
- 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. This evaluation should exclude the presence of genital or breast neoplasia unless the patient is to be treated with PROVERA for recurrent endometrial, breast or renal cancer.

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, 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.

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 medroxyprogesterone possesses adrenocorticoid activity.

Observational and randomised, prospective trials on the long-term effects of a combined estrogen/progestogen 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.

Breast cancer

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.

Ovarian cancer

Current use of estrogen only or estrogen plus progestogen products in post-menopausal women for 5 or more years has been associated with an increased risk of ovarian cancer.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Use of combined estrogen/progestogen 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 re-examining the patient.

Decrease in BMD

There are no studies on the BMD effects of PROVERA. However, 2 clinical studies of adult women of childbearing potential and of adolescent females given MPA 150 mg IM every 3 months, for contraception, demonstrated a statistically significant decrease in BMD (see CLINICAL TRIALS). Decreases in serum estrogen 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.

Bone loss may be greater with increasing duration of use and may not be completely reversible in some women. It is unknown if use of MPA during adolescence and early adulthood, a critical period of bone accretion, will reduce peak bone mass. In both adult and adolescent females, the decrease in BMD during treatment appears to be substantially reversible after MPA IM injection is discontinued and ovarian estrogen production increases. After discontinuing MPA IM injection in adolescents, full recovery of mean BMD required 1 year at the lumbar spine and approximately 3 years at the total hip (see CLINICAL TRIALS).

In adults, BMD was observed for a period of 2 years after MPA IM injection was discontinued and partial recovery of mean BMD towards baseline was observed at total hip, femoral neck and lumbar spine (see CLINICAL TRIALS). A large observational study of female

contraceptive users showed that use of MPA IM injection has no effect on a woman's risk for osteoporotic or non-osteoporotic fractures.

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.

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. 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.

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.

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 progestogens therapy when relevant specimens are submitted.

Weight changes

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

General

The high doses of PROVERA 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.

Effects on fertility

MPA given orally at 1 mg/kg/day, 10 mg/kg/day 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.

Use in pregnancy: Category D

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

If PROVERA is used during pregnancy, or if the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential risk to the fetus (see CONTRAINDICATIONS).

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

NOTE: In peri-menopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of HRT. An endometrial biopsy may be performed at the discretion of the attending physician.

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 estrogens and MPA. 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.

Carcinogenicity

Long-term toxicology studies in the monkey, dog and rat with parenteral MPA have disclosed:

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 2 high dose animals that developed breast malignancies.

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 3 of the monkeys in the 30 mg/kg group. Upon histopathological examination these nodules were determined to be hyperplastic.

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.

Effects on laboratory tests

The following laboratory tests may be affected by the use of PROVERA:

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

- plasma estrogen levels (in the female)
- sex hormone-binding globulin
- plasma cortisol levels
- glucose tolerance test
- metyrapone test - the use of MPA 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 adrenocorticotrophic hormone should be demonstrated before metyrapone is administered.

INTERACTIONS WITH OTHER MEDICINES

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

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 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 have been associated with the use of progestogens including MPA:

Cardiac disorders: myocardial infarction, congestive heart failure, palpitations, tachycardia.

Endocrine disorders: corticoid-like effects (e.g., Cushingoid syndrome), prolonged anovulation.

Eye disorders: retinal embolism and thrombosis, diabetic cataract, visual impairment.

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, dry mouth.

General disorders and administration site conditions: oedema/fluid retention, pyrexia, malaise, fatigue.

Hepatobiliary disorders: jaundice, jaundice cholestatic, liver function abnormal (transient elevations of alkaline phosphatase and/or serum transaminase activities).

Immune system disorder: anaphylactic reaction, drug hypersensitivity, anaphylactoid reaction, angioedema.

Investigations: decreased glucose tolerance, increased blood pressure, liver function test abnormal, increases in white cell, increased platelet count, elevation of serum calcium and potassium levels, weight increased, weight decreased.

Metabolic and nutritional disorders: exacerbation of diabetes mellitus, hypercalcaemia, weight fluctuation, changes in appetite.

Musculoskeletal and connective tissue disorders: muscle spasms.

Nervous system disorders: dizziness, headache, loss of concentration, somnolence, cerebral infarction, adrenergic-like effects (e.g., fine-hand tremors, cramps in calves at night), tremors.

Psychiatric disorders: depression, insomnia, confusion, nervousness, euphoria, changes in libido. Some patients may complain of premenstrual-like depression while on PROVERA.

Renal and urinary system disorders: glycosuria.

Reproductive system and breast disorders: dysfunctional uterine bleeding (irregular, increase, decrease, spotting), galactorrhoea, amenorrhoea, cervical discharge, changes in cervical excretions and secretions, uterine cervical erosion, breast tenderness, breast pain.

The use of estrogens and progestogens by post-menopausal women has been associated with an increased risk of breast cancer (see PRECAUTIONS).

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.

Post-marketing experience

The following adverse events have been reported during post-marketing experience.

Reproductive system and breast disorders: There have been post-marketing reports of erectile dysfunction in association with use of MPA in oncology treatments.

Skin and subcutaneous tissue disorders: lipodystrophy acquired.

DOSAGE AND ADMINISTRATION

Inoperable, recurrent, metastatic, endometrial carcinoma

200 mg to 400 mg daily.

Breast carcinoma

500 mg daily until progression of disease.

Renal cell carcinoma

200 mg to 400 mg daily.

Endometriosis

Beginning the first day of the menstrual cycle 10 mg 3 times daily for 90 consecutive days.

Secondary amenorrhoea not due to pregnancy

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

In amenorrhoea associated with a poorly developed proliferative endometrium, conventional estrogen therapy may be employed in conjunction with 5 mg to 10 mg daily for 10 days.

Abnormal uterine bleeding in the absence of organic pathology

2.5 mg to 10 mg daily for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Treatment should be repeated for 3 consecutive cycles.

Adjunct to estrogen therapy#

10 mg to 20 mg per day for at least 10 days of each cycle or 5 mg per day continuously for 28 days of each cycle.

#Use of combined estrogen/progestogen 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 re-examining the patient.

OVERDOSAGE

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

PROVERA tablets are available as:

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

5 mg tablets: blue, circular, scored on one side and marked 286 on both sides of the score line, 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.

+ Not all strengths and presentations may be available.

Storage conditions

Store below 30ºC.

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)

100 mg, 200 mg, 250 mg and 500 mg tablets: 2 August 1991.

2.5 mg, 5 mg and 10 mg tablets: 7 January 1993.

DATE OF MOST RECENT AMENDMENT

07 March 2017.

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