PROVERA®

Medroxyprogesterone Acetate

Provera 5mg Tablets

Reference market: UK

AfME Markets using same as LPD:

Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROVERA 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA 5 mg Tablets

Each tablet contains:

Active ingredient: medroxyprogesterone acetate 5.0 mg;
Excipients with known effects: **lactose monohydrate, sucrose**

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Progestogen. Indicated for dysfunctional (anovulatory) uterine bleeding, secondary amenorrhoea and for mild to moderate endometriosis.

4.2 Posology and method of administration

Posology

Adults:
Dysfunctional (anovulatory) uterine bleeding: 2.5 - 10 mg daily for 5 - 10 days commencing on the assumed or calculated 16th - 21st day of the cycle. Treatment should be given for two consecutive cycles. When bleeding occurs from a poorly developed proliferative endometrium, conventional oestrogen therapy may be employed in conjunction with medroxyprogesterone acetate in doses of 5 - 10 mg for 10 days.

Secondary amenorrhoea: 2.5 - 10 mg daily for 5 - 10 days beginning on the assumed or calculated 16th to 21st day of the cycle. Repeat the treatment for three consecutive cycles. In amenorrhoea associated with a poorly developed proliferative endometrium, conventional oestrogen therapy may be employed in conjunction with medroxyprogesterone acetate in doses of 5 - 10 mg for 10 days.

Mild to moderate endometriosis: Beginning on the first day of the menstrual cycle, 10 mg three times a day for 90 consecutive days. Breakthrough bleeding, which is self-limiting, may occur. No additional hormonal therapy is recommended for the management of this bleeding.

Elderly: Not applicable

Paediatric population: Not applicable

Method of administration

For oral use.

4.3 Contraindications

Known or suspected pregnancy;

Known, past or suspected breast cancer;

Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);

Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal;

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Porphyria

4.4 Special warnings and precautions for use

Medical Examination/Follow-Up

Before initiating or reinstituting therapy, a complete personal and family medical history should be taken. Physical (including pelvic) examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman, but may include, if judged appropriate by the clinician, abdominal and pelvic examination. Women should be encouraged to participate in the national breast cancer screening programme (mammography) and the national cervical screening programme (cervical cytology) as appropriate for their age.

The possibility of genital tract pathology should be considered before commencing treatment in women with abnormal uterine bleeding, especially in women over 45, who may require gynaecological investigation.
A negative pregnancy test should be demonstrated before starting therapy (see section 4.6).

Doses of up to 30 mg a day may not suppress ovulation and patients should be advised to take adequate contraceptive measures, where appropriate.

Conditions which need Supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Provera, in particular:

- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1 degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus.
- Epilepsy
- Asthma
- Otosclerosis

Rare cases of thrombo-embolism have been reported with use of Provera, especially at higher doses. Causality has not been established.

History or emergence of the following conditions require careful consideration and appropriate investigation: signs of a blood clot; migraine or unusually severe headaches or acute visual disturbances of any kind.

Provera, especially in high doses, may cause weight gain and fluid retention. With this in mind, caution should be exercised in treating any patient with a pre-existing medical condition, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, that might be adversely affected by weight gain or fluid retention.

Some patients receiving Provera may exhibit a decreased glucose tolerance. The mechanism for this is not known. This fact should be borne in mind when treating all patients and especially known diabetics.

This product contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients with a history of treatment for mental depression should be carefully monitored while receiving Provera therapy. Some patients may complain of premenstrual like depression while on Provera therapy.

Reasons for Immediate Withdrawal of Therapy:

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglutethimide administered concurrently with Provera may significantly depress the bioavailability of Provera.

Interactions with other medicinal treatments (including oral anti-coagulants) have rarely been reported, but causality has not been determined. The possibility of interaction should be borne in mind in patients receiving concurrent treatment with other drugs.
The metabolism of progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Medroxyprogesterone acetate (MPA) is metabolized in-vitro primarily by hydroxylation via the CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of progestogens.

Clinically, an increased metabolism of progestogens may lead to decreased effect.

4.6 Fertility, pregnancy and lactation

Fertility
MPA at oral doses may inhibit ovulation.

Women may experience a delay in return to fertility (conception) following discontinuation of Provera.

Pregnancy

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.
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.

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.

Breast-feeding

Medroxyprogesterone acetate and its metabolites are secreted in breast milk. In nursing mothers treated with medroxyprogesterone acetate injection 150 mg IM every 3 months, milk composition, quality, and amount are not adversely affected
Neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioural effects through puberty. No adverse effects have been noted.
However, due to limitations of the data regarding the effects of MPA in breastfed infants less than six weeks old, Provera should be given no sooner than six weeks post-partum when the infant's enzyme system is more developed.

4.7 Effects on ability to drive and use machines

No adverse effect has been reported.

4.8 Undesirable effects

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from Phase 3 clinical studies that evaluated efficacy and safety of DMPA in gynaecology. Those most frequently (>5%) reported adverse drug reactions were dysfunctional uterine bleeding (19%), headache (12%) and nausea (10%).

The following lists of adverse reactions are listed within the organ system classes, under headings of frequency (number of patients expected to experience the reaction), using the following categories:
Very common (≥1/10)
Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100);
Rare (≥1/10,000 to <1/1000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

System Organ Class	Very Common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Very Rare < 1/10,000	Frequency Not Known (cannot be estimated from available data)
Immune system disorders		Drug hypersensitivity				Anaphylactic reaction, Anaphylactoid reaction, Angioedema
Endocrine disorders						Anovulation
Psychiatric disorders		Depression, Insomnia, Nervousness				
Nervous system disorders	Headache	Dizziness				Somnolence

Vascular disorders						Embolism and thrombosis
Gastrointestinal disorders	Nausea					
Skin and subcutaneous tissue disorders		Alopecia, Acne, Urticaria Pruritus	Hirsutism			Rash
Reproductive system and breast disorders	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)	Cervical discharge, Breast pain, Breast tenderness	Galactorrhoea			Amenorrhoea, Uterine cervical erosion
General disorders and administration site conditions		Temperature elevation, Fatigue	Oedema, Fluid retention			
Investigations		Weight increased				Glucose tolerance decreased, Weight decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation 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 according to their local country requirements.

Saudi Arabia :

To report any side effect(s):

National Pharmacovigilance Center (NPC)

- Fax: +966 11 205 7662
- Call NPC at 00966 11 2038222, Exts: 2317-2356-2340
- Call center :19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

4.9 Overdose

In animals Provera has been shown to be capable of exerting an adreno-corticoid effect, but this has not been reported in the human, following usual dosages. The oral administration of Provera at a rate of 100 mg per day has been shown to have no effect on adrenal function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens – Pregnen (4) derivatives, ATC code: G03DA02

Medroxyprogesterone acetate has actions and uses similar to those of progesterone.

MPA has minimal androgenic activity compared to progesterone and virtually no oestrogenic activity.

Progestogens are used in the treatment of dysfunctional uterine bleeding, secondary amenorrhoea and endometriosis.

5.2 Pharmacokinetic properties

MPA is rapidly absorbed from the G-I tract with a single oral dose of 10-250 mg. The time taken to reach the peak serum concentration (T_{max}) was 2-6 hours and the average peak serum concentration (C_{max}) was 13-46.89 mg/ml.

Unmetabolised MPA is highly plasma protein bound. MPA is metabolised in the liver.

MPA is primarily metabolised by faecal excretion as glucuronide conjugated metabolite.

Metabolised MPA is excreted more rapidly and in a greater percentage following oral doses than after aqueous intramuscular injection

5.3 Preclinical safety data

None stated

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PROVERA 5 mg Tablets: lactose monohydrate, talc, maize starch, **sucrose**, calcium stearate, liquid paraffin, indigotin (E132), aluminium oxide hydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use Provera after the expiry date which is stated on the carton after EXP:. The expiry date refers to the last day of that month.

Shelf life: 36 months.

6.4 Special precautions for storage

Do not Store above 30 °C
Do not refrigerate

6.5 Nature and contents of container

Pale blue, round tablets. The tablets are supplied in High-density polyethylene (HDPE) bottle closed with polypropylene (PP) cap with an inner seal and cotton coil.

Pack size: 24 tablets.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Any unused product or waste material should be disposed in accordance with local requirements.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer Italia S.r.l. via Isonzo, 71-04100 Latina, Italy

Manufacturer

Pfizer Italia S.r.l.
Località Marino del Tronto
63100 Ascoli Piceno (AP), Italy

8. MARKETING AUTHORISATION NUMBER

28-44-89

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

01-May-1988

10. DATE OF REVISION OF THE TEXT

February 2020

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers

Union of Arabic Pharmacists