



## **PROVERA**

Medroxyprogesterone acetate

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

Each tablet contains 5 mg medroxyprogesterone acetate.

### Excipients with known effect:

Lactose monohydrate 84.2 mg, sucrose 1.465 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

## 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

Meningiomas have been reported following long term administration of progestogens, including medroxyprogesterone acetate. Provera should be discontinued if a meningioma is diagnosed. Caution is advised when recommending Provera to patients with a history of meningioma.

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 fetuses.

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 ( $\geq 1/10$ )*

*Common ( $\geq 1/100$  to  $< 1/10$ );*

*Uncommon ( $\geq 1/1000$  to  $< 1/100$ );*

*Rare ( $\geq 1/10,000$  to  $< 1/1000$ );*

*Very rare ( $< 1/10,000$ );*

*Not known (cannot be estimated from the available data).*

| System Organ Class                                   | Very Common<br>≥1/10   | Common<br>≥ 1/100 to<br>< 1/10                           | Uncommon<br>≥ 1/1000 to<br>< 1/100 | Rare ≥<br>1/10,000<br>to <<br>1/1000 | Very<br>Rare<br><<br>1/10,000 | Frequency Not<br>Known (cannot<br>be estimated<br>from available<br>data) |
|--|--|--|------------------------------------|--------------------------------------|-------------------------------|---|
| Immune system disorders                              |  | Drug hypersensitivity                                    |                                    |                                      |                               | Anaphylactic reaction,<br>Anaphylactoid reaction,<br>Angioedema           |
| Endocrine disorders                                  |  |  |                                    |                                      |                               | Anovulation   |
| Psychiatric disorders                                |  | Depression,<br>Insomnia,<br>Nervousness                  |                                    |                                      |                               |   |
| Nervous system disorders                             | Headache   | Dizziness  |                                    |                                      |                               | Somnolence  |
| Vascular disorders                                   |  |  |                                    |                                      |                               | Embolism and thrombosis   |
| Gastrointestinal disorders                           | Nausea   |  |                                    |                                      |                               |   |
| Skin and subcutaneous tissue disorders               |  | Alopecia, Acne,<br>Urticaria<br>Pruritus                 | Hirsutism                          |                                      |                               | Rash  |
| Reproductive system and breast disorders             | Dysfunctional uterine bleeding (irregular, increase, decrease, spotting) | Cervical discharge,<br>Breast pain,<br>Breast tenderness | Galactorrhoea                      |                                      |                               | Amenorrhoea,<br>Uterine cervical erosion                                  |
| General disorders and administration site conditions |  | Temperature elevation,<br>Fatigue                        | Oedema, Fluid retention            |                                      |                               |   |
| Investigations                                       |  | Weight increased   |                                    |                                      |                               | Glucose tolerance decreased,<br>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.

#### To report any side effect(s):

- **Saudi Arabia:**

**National Pharmacovigilance Center (NPC)**

- Call center: 19999
- E-mail: [npc.drug@sfd.gov.sa](mailto:npc.drug@sfd.gov.sa)
- Website: <https://ade.sfd.gov.sa/>

- **Other GCC States**

- Please contact the relevant competent authority.

#### **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**

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 medicinal product or waste material should be disposed of 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 INFORMATIONMARKETING 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. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

Date of first authorisation: 01-May-1988

### **9. DATE OF REVISION OF THE TEXT**

May 2024



