

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Trade Name of the Medicinal Products

Provera Tablets 5 mg

### 2. Qualitative and Quantitative Composition

Each tablet contains 5 mg medroxyprogesterone acetate (MPA).

### 3. Pharmaceutical Form

Tablets for oral use.

### 4. Clinical Particulars

#### 4.1 Therapeutic indications

Indicated for cases requiring progesterone supplement.

#### 4.2 Posology and method of administration

Oral.

#### *Gynecology*

Use of combined estrogen/progestin therapy in postmenopausal women should be limited to the lowest effective dose and shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically evaluated. (see **Section 4.4 – Special warnings and precautions for use.**)

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestin in a woman without an intact uterus.

#### *Endometriosis*

- Oral MPA 10 mg three times per day for 90 consecutive days, beginning on the first day of the menstrual cycle.

#### *Menopausal Vasomotor Symptoms*

- Oral MPA 10 to 20 mg per day given continuously.

### *Diagnosis of Primary and Secondary Amenorrhea*

- Oral MPA 2.5 to 10 mg per day for 5 to 10 days.

### *Treatment of Secondary Amenorrhea*

- Oral MPA 2.5 to 10 mg daily for 5 to 10 days, for 3 consecutive cycles. In patients with hypotrophy of the endometrium, estrogens should be used concomitantly with MPA therapy.

### *Dysfunctional (Anovulatory) Uterine Bleeding*

- Oral MPA 2.5 to 10 mg per day for 5 to 10 days for 2 to 3 cycles and then discontinued to see if the dysfunction has regressed. If bleeding occurs from a poorly proliferative endometrium, estrogens should be used concomitantly with MPA therapy.

### *Opposition of endometrial effects of estrogen in menopausal women being treated with estrogen (Hormone Therapy [HT])*

For women taking 0.625 mg of conjugated estrogen or an equivalent daily dose of another estrogen, MPA can be given in one of two regimens:

- Continuous regimen of MPA - Oral MPA 2.5 to 5.0 mg daily.
- Sequential regimen of MPA - Oral MPA 5 to 10 mg daily for 10 to 14 consecutive days of a 28-day or monthly cycle.

*Elderly:* Not applicable

*Children:* Not applicable

## **4.3 Contra-indications**

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);

Undiagnosed vaginal bleeding

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

Known hypersensitivity to the active substances or to any of the excipients;

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. Discontinuation of MPA is recommended in patients who develop VTE while undergoing therapy with MPA.

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.

Unexpected vaginal bleeding during therapy with MPA should be investigated.

#### 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).

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**

##### **Pregnancy**

Provera is not indicated during pregnancy. If pregnancy occurs during medication with Provera, treatment should be withdrawn immediately.

Some reports suggest under certain circumstances, an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in fetuses.

##### **Lactation**

Provera is not indicated during lactation.

Medroxyprogesterone acetate and its metabolites are secreted in breast milk, but there is no evidence to suggest that this presents any hazard to the child.

#### **4.7 Effects on ability to drive and use machines**

The effect of medroxyprogesterone acetate on the ability to drive and use machinery has not been systematically evaluated.

#### 4.8 Undesirable effects

The following medical events have been occasionally to rarely associated with the use of progestogens:

MEDDRA SOC	EVENT
Immune System disorders	Hypersensitivity reactions (e.g., anaphylaxis & anaphylactoid reactions, angioedema)
Endocrine disorders	Prolonged anovulation
Metabolism and nutritional disorders	Weight change, oedema/fluid retention
Psychiatric disorders	Depression, insomnia, nervousness
Nervous system disorders	Dizziness, headache, somnolence
Vascular disorders	Thromboembolic disorders
Gastrointestinal disorders	Nausea
Hepatobiliary disorders	Cholestatic icterus/jaundice
Skin and subcutaneous tissue disorders	Acne, alopecia, hirsutism, pruritus, rash, urticaria
Reproductive system and breast disorders	Abnormal uterine bleeding (irregular, increase, decrease), amenorrhea, cervical erosions, galactorrhoea, mastodynia, breast tenderness, breast pain
General disorders and administration site conditions	Fatigue
Investigations	Alterations of cervical secretions, decreased glucose tolerance

#### 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.

Oral doses up to 3 g per day have been well tolerated. Overdose treatment is symptomatic and supportive.

### Pharmacological Properties

#### 5.1 Pharmacodynamic properties

Medroxyprogesterone acetate (17a-hydroxy-6a-methylprogesterone acetate) is a derivative of progesterone.

### *Mechanism of Action*

MPA is a synthetic progestin (structurally related to the endogenous hormone progesterone) which has been demonstrated to possess several pharmacologic actions on the endocrine system:

- Inhibition of pituitary gonadotropins (FSH and LH);
- Decrease of ACTH and hydrocortisone blood levels;
- Decrease of circulating testosterone;
- Decrease of circulating estrogen levels (as the result of both FSH inhibition and enzymatic induction of hepatic reductase, resulting in increased clearance of testosterone and consequent decreased conversion of androgens to estrogens).

All of these actions result in a number of pharmacological effects as described below.

### *Gynecology*

Medroxyprogesterone acetate (MPA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered DMPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

### *Endometriosis*

Suppression of serum estradiol concentrations and a possible direct action of DMPA-SC on the lesions of endometriosis are likely to be responsible for the therapeutic effect on endometriosis-associated pain.

## **5.2 Pharmacokinetic properties**

Absorption: Oral MPA is rapidly absorbed with maximum concentration obtained between 2 to 4 hours. The half-life of oral MPA is approximately 17 hours. It is 90% protein bound, and is mainly excreted in the urine.

Administration with food increases the bioavailability of MPA. A 10 mg dose of oral MPA, taken immediately before or after a meal, increased average MPA  $C_{max}$  (51% and 77%, respectively) and average AUC (18% and 33%, respectively). The half-life of MPA was not changed with food.

*Distribution:* MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex-hormone-binding globulin. The unbound MPA modulates pharmacologic responses.

*Metabolism:* Following oral dosing, MPA is extensively metabolized in the liver via ring A and/or side-chain hydroxylation, with subsequent conjugation and elimination in the urine. At least 16 MPA metabolites have been identified. In a study designed to measure the metabolism of MPA, the results suggest that human cytochrome P450 3A4 is primarily involved in the overall metabolism of MPA in human liver microsomes.

*Elimination:* Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. Mean percent dose excreted in the 24-hour urine of patients with fatty liver as intact MPA after a 10 mg or 100 mg dose was 7.3% and 6.4%, respectively. Elimination half-life of oral MPA is 12 to 17 hours.

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

### **5.3 Preclinical Safety Data**

There was no evidence of a carcinogenic effect associated with the oral administration of oral MPA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of in vitro or in vivo genetic toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

## **Pharmaceutical Particulars**

### **6.1 List of excipients**

Lactose, Maize Starch, Sucrose, Liquid Paraffin (Mineral oil), Calcium Stearate, Talc, FD & C Blue No. 2 Aluminium Lake.

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf-life**

60 months if stored in amber glass bottles.  
36 months if stored in blister strips.



#### **6.4 Special precautions for storage**

Store below 25°C.

#### **6.5 Nature and contents of container**

Blister strips containing 100 tablets or amber glass bottles with screw caps containing 24 tablets.

Not all pack sizes may be marketed.

***Manufacturer:*** Pfizer Italia S.r.l

***License holder:*** Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Hertzliya Pituach, 46725.