SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Products

Provera 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);

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 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			

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)
Investigations		Weight increased				Glucose tolerance decreased, Weight decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blister strips containing 100 tablets or a bottle containing 24 tablets.
Not all pack sizes may be marketed.

7 License holder

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8 License Number

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