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

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Provera 100 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 100mg medroxyprogesterone acetate (MPA).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Progestogen indicated for the treatment of certain hormone dependent neoplasms.

4.2 Posology and method of administration

Route of administration: Oral.

Adults
Recurrent and/or Metastatic Endometrial or Renal Cancer 100 - 600 mg daily

Recurrent and/or Metastatic Breast Cancer 400 - 1500 mg daily

Metastatic Prostate Cancer 100 - 500 mg daily

The incidence of minor side-effects, such as indigestion and weight gain, increase with the increase in dose.

Response to hormonal therapy may not be evident until after at least 8-10 weeks of therapy.

Elderly patients: This product has been used primarily in the older age group for the treatment of malignancies. There is no evidence to suggest that the older age group is any less prepared to handle the drug metabolically than is the younger patient. Therefore the same dosage, contra-indications, and precautions would apply to either age group.

Children: The product is not anticipated for paediatric use in the indications recommended.

4.3 Contra-indications

Medroxyprogesterone acetate is contraindicated in the following conditions:

- thrombophlebitis, thrombo-embolic disorders, and where there is a high risk of developing such manifestations [presence or history of atrial fibrillation, valvular disorders, endocarditis, heart failure, pulmonary embolism; thrombo-embolic ischaemic attack (TIA), cerebral infarction; atherosclerosis; immediate post surgery period]
- hypercalcaemia in patients with osseous metastases
- known sensitivity to medroxyprogesterone acetate or any component of the drug.
- impaired liver function or active liver disease.
- missed abortion, metrorrhagia, known or suspected pregnancy.
- undiagnosed vaginal bleeding.
- previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism).
- active or recent arterial thromboembolic disease (e.g., angina, myocardial infarction).
- suspected or early breast carcinoma.

Progestogens are known to be porphyrogenic. Patients with a history of attacks or aged under 30 are at greatest risk of an acute attack while on progesterone treatment. A careful assessment of potential benefit should be made where this risk is present.

4.4 Special Warnings and Precautions for Use

Warnings:

In the treatment of carcinoma of breast occasional cases of hypercalcaemia have been reported.

Unexpected vaginal bleeding during therapy with medroxyprogesterone acetate should be investigated.

Medication should not be readministered 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 not be readministered.

Medroxyprogesterone acetate may produce Cushingoid symptoms.

Some patients receiving medroxyprogesterone acetate may exhibit suppressed adrenal function. Medroxyprogesterone acetate may decrease ACTH and hydrocortisone blood levels.

Treatment with medroxyprogesterone acetate should be discontinued in the event of:

- jaundice or deterioration in liver function
- significant increase in blood pressure
- new onset of migraine-type headache

Precautions:

Animal studies show that Provera possesses adrenocorticoid activity. This has also been reported in man, therefore patients receiving large doses continuously and for long periods should be observed closely for signs normally associated with adrenocorticoid therapy, such

as hypertension, sodium retention, oedema, etc. Care is needed in treating patients with diabetes and/or arterial hypertension.

Before using Provera the general medical condition of the patient should be carefully evaluated.

This product should be used under the supervision of a specialist and the patient kept under regular surveillance.

Patients with the following conditions should be carefully monitored while taking progestogens:

- Conditions which may be influenced by potential fluid retention
  - Epilepsy
  - Migraine
  - Asthma
  - Cardiac dysfunction
  - Renal dysfunction
- History of mental depression
- Diabetes (a decrease in glucose tolerance has been observed in some patients).
- Hyperlipidaemia

The pathologist (laboratory) should be informed of the patient's use of medroxyprogesterone acetate if endometrial or endocervical tissue is submitted for examination.

The physician/laboratory should be informed that medroxyprogesterone acetate may decrease the levels of the following endocrine biomarkers:

- Plasma/urinary steroids (e.g., cortisol, oestrogen, pregnanediol, progesterone, testosterone)
- Plasma/urinary gonadotrophins (e.g., LH and FSH)
- Sex-hormone-binding-globulin

The use of medroxyprogesterone acetate in oncology indications may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during Metyrapone testing. Thus the ability of adrenal cortex to respond to ACTH should be demonstrated before metyrapone is administered.

Although medroxyprogesterone acetate has not been causally associated with the induction of thromboembolic disorders, MPA is not recommended in any patient with a history of venous thromboembolism (VTE). Discontinuation of medroxyprogesterone acetate is recommended in patients who develop VTE while undergoing therapy with MPA.

Risk of venous thromboembolism (VTE)

The risk of VTE has not been assessed for progesterone alone. However, VTE is a known risk factor of oestrogen-only and combined hormone replacement therapy. When prescribing medroxyprogesterone acetate for oncology indications the following precautions and risk factors should be considered in the light of the patient's condition, the dose of medroxyprogesterone acetate and the duration of therapy:

- Generally recognised risk factors for VTE include a personal or family history of VTE or known thromboembolic states, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery.
- If VTE develops after initiating therapy, medroxyprogesterone acetate should be discontinued. Patients should be told to contact their doctor immediately if they become

aware of a symptom suggestive of potential thromboembolism (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

4.5 Interaction with other Medicinal Products and other forms of Interaction

Interaction with other medicaments

The metabolism of progestogens may be increased by concomitant administration of compounds known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes. These compounds include 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. Progestogen levels may therefore be reduced.

Aminoglutethimide has been reported to decrease plasma levels of some progestogens.

Concurrent administration of ciclosporin and MPA has been reported to lead to increased plasma ciclosporin levels and/or decreased plasma MPA levels.

Interactions with oral anti-coagulants have been reported rarely, but causality has not been established.

When used in combination with cytotoxic drugs, it is possible that progestogens may reduce the haematological toxicity of chemotherapy.

Special care should be taken when progestogens are administered with other drugs which also cause fluid retention, such as NSAIDs and vasodilators.

Other forms of interaction

Progestogens can influence certain laboratory tests (e.g., tests for hepatic function, thyroid function and coagulation).

4.6 Pregnancy and Lactation

Pregnancy

Medroxyprogesterone acetate is contraindicated in women who are pregnant. If medroxyprogesterone acetate 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.

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.

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.

Lactation

Medroxyprogesterone acetate and/or its metabolites are secreted in breast milk. Therefore, the use of Provera whilst breast-feeding is not recommended.

4.7 Effects on Ability to Drive and Use Machines

The effect of MPA on the ability to drive and use machines has not been systematically evaluated.

4.8 Undesirable Effects

Reactions occasionally associated with the use of progestogens, particularly in high doses, are:

Breast: Tenderness, mastodynia or galactorrhoea.

Genitourinary: Abnormal uterine bleeding (irregular, increase, decrease), amenorrhoea, alterations of cervical secretions, cervical erosions, prolonged anovulation.

Central nervous system: Confusion, euphoria, loss of concentration, nervousness, insomnia, somnolence, fatigue, dizziness, depression, vision disorders and headache.

Skin and mucous membranes: Sensitivity reactions ranging from pruritus, urticaria, angioneurotic oedema, to generalised rash and anaphylaxis have occasionally been reported. Acne, alopecia or hirsutism have been reported in a few cases.

Allergy: Hypersensitivity reactions (e.g., anaphylaxis or anaphylactoid reactions, angioedema).

Gastro-intestinal/hepatobiliary: Constipation, diarrhoea, dry mouth, disturbed liver function, jaundice, vomiting, nausea and indigestion .

Metabolic and nutritional: Adrenergic-like effects (e.g., fine hand tremors, sweating, tremors, cramps in calves at night), corticoid-like effects (e.g., Cushingoid Syndrome), decreased glucose tolerance, diabetic cataract, exacerbation of diabetes mellitus, glycosuria.

Cardiovascular: Cerebral and myocardial infarction, congestive heart failure, increased blood pressure, palpitations, pulmonary embolism, retinal thrombosis, tachycardia, thromboembolic disorders, thrombophlebitis.

Haematological: Elevation of white blood cells and platelet count.

Miscellaneous: Change in appetite, change in libido, oedema/fluid retention, hypercalcaemia, malaise, hyperpyrexia, weight gain, moon facies.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens. ATC Code: L02A B

Medroxyprogesterone acetate has the pharmacological action of a progestogen.

MPA is a synthetic progestin (structurally related to the endogenous hormone progesterone), which has been demonstrated to possess several pharmacological 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.

Oncology

MPA demonstrates antitumor activity. When MPA is given to patients at high doses (either by the oral route or by intramuscular injection) it is effective in the palliative treatment of hormone-responsive, malignant neoplasms.

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 Cmax (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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Maize Starch
Hydrolyzed gelatine (Byco C)
Polyethylene glycol (Macrogol 400)
Sodium starch glycollate (Type A)
Sodium decosate
Sodium benzoate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at temperature not exceeding 25°C. Bottle pack only: keep in a well closed container.

6.5 Nature and contents of container

100 tablets in glass bottle or blister.

Manufacturer: Pfizer Italia S.r.l, Localita Marino del Tronto, 63100 Ascoli Piceno, Italy.

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