Provera® Tablet 100 mg
Medroxyprogesterone Acetate

1. NAME OF THE MEDICINAL PRODUCT

Provera Tablets 100 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg medroxyprogesterone acetate.

Excipient with known effect:
Each tablet contains 0.139 mg sodium benzoate.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Progestogen is indicated for the treatment of certain hormone dependant neoplasms, such as:

1. Endometrial carcinoma.
2. Renal cell carcinoma.
3. Carcinoma of breast in post-menopausal women.

4.2 Posology and method of administration

Posology

Adults

Endometrial and renal cell carcinoma	200 - 600 mg daily
Breast carcinoma	400 - 1500 mg daily

The incidence of minor side-effects, such as indigestion and weight gain, increases with 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, contraindications, and precautions would apply to either age group.

Paediatric population
The product is not anticipated for paediatric use in the indications recommended.

Method of administration
For Oral use.

4.3 Contraindications

Medroxyprogesterone acetate is contraindicated in the following conditions:

- thrombophlebitis, thromboembolic 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; thromboembolic ischaemic attack (TIA), cerebral infarction; atherosclerosis; immediate post-surgery period]
- hypercalcaemia in patients with osseous metastases
- hypersensitivity to the active substance or to any of the excipients
- 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 porphyrinogenic. 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 re-administered 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 re-administered.

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, any patient with a history or who develops this kind of event while undergoing therapy with medroxyprogesterone acetate should have her status and need for treatment carefully assessed before continuing therapy.

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)

<u>Excipient Information</u>
Each 100 mg tablet contains 0.139 mg sodium benzoate (see section 2). Benzoates may increase unconjugated bilirubin levels by displacing bilirubin from albumin, which may increase neonatal jaundice. Neonatal hyperbilirubinaemia may lead to kernicterus (non-conjugated bilirubin deposits in the brain tissue) and encephalopathy. However, this medicinal product is

not indicated for use in children and this warning is only included for completeness.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products
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.

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.

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

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/or 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 1337 patients who received MPA in 4 pivotal studies that evaluated efficacy and safety of MPA for oncology indications.

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			Angioedema	Drug hypersensitivity		Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders			Corticoid-like effects			Prolonged anovulation
Metabolism and nutritional disorders		Weight fluctuation, Increased appetite	Diabetes mellitus exacerbated, Hypercalcaemia			

Psychiatric disorders		Insomnia	Depression, Euphoria, Changes in libido	Nervousness		Confusion
Nervous system disorders		Headache, Dizziness, Tremors		Cerebral infarction, Somnolence		Loss of concentration, Adrenergic-like effects
Eye disorders						Retinal embolism and thrombosis, Cataract diabetic, Visual impairment
Cardiac disorders			Cardiac failure congestive	Myocardial infarction		Tachycardia, Palpitations
Vascular disorders			Thrombophlebitis	Embolism and thrombosis		
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism			
Gastrointestinal disorders		Vomiting, Constipation, Nausea	Diarrhoea, Dry mouth			
Hepatobiliary disorders				Jaundice		
Skin and subcutaneous tissue disorders		Hyperhidrosis	Acne, Hirsutism	Alopecia, Rash		Urticaria, Pruritus
Musculoskeletal and connective tissue disorders			Muscle spasms			
Renal and urinary system disorders						Glycosuria
Reproductive system and breast disorders		Erectile dysfunction	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), Breast pain			Amenorrhoea, Uterine cervical erosions, Cervical discharge, Galactorrhoea
General disorders and administration site conditions		Oedema/fluid retention, Fatigue		Malaise, Pyrexia		
Investigations				Glucose tolerance decreased, Blood pressure increased		Liver function test abnormal, White blood cell count increased, Platelet count increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

No action required other than cessation of therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens. ATC Code: L02AB02

Medroxyprogesterone acetate has the pharmacological action of a progestogen.

5.2 Pharmacokinetic properties

Medroxyprogesterone acetate is absorbed from the gastro-intestinal 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 medroxyprogesterone acetate is highly plasma protein bound. Medroxyprogesterone acetate is metabolised in the liver.

Medroxyprogesterone acetate is primarily metabolised by faecal excretion as glucuronide conjugated metabolite.

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

5.3 Preclinical safety data

No further preclinical safety data available.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not applicable.

6.2 Shelf-life

Please refer to the outer carton for expiry date.

6.3 Special precautions for storage

Please refer to the outer carton for storage condition.

6.4 Special precautions for disposal and other handling

No special requirements.

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