Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Provera 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of medroxyprogesterone acetate

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

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White, round flat tablets marked 'U-467' on one side and scored on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a progestogenic agent in the treatment of hormone-dependent neoplasms such as endometrial carcinoma and renal cell carcinoma, and carcinoma of the breast in post menopausal women.

4.2 Posology and method of administration

Posology

Endometrial and renal cell carcinoma:

The usual total daily dose is 200 to 400 mg.

Breast carcinoma:

The usual total daily dose is 400 to 800 mg. The incidence of side effects increases with doses to 1000 mg.

Treatment may be required for 8-10 weeks before an assessment of response can be made.

Method of administration
For oral use.

4.3 Contraindications

Use in patients with liver dysfunction or disease.

Use in patients with thromboembolic disorders or a history thereof.

Use in patients that are known or suspected to be pregnant.

Use in patients with undiagnosed vaginal bleeding.

Hypersensitive to the active substance medroxyprogesterone acetate or to any of the excipients of this medicine listed in section 6.1.

4.4 Special warnings and precautions for use

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 patients should be kept under regular surveillance.

Decrease in Bone Mineral Density

There are no studies on the bone mineral density (BMD) effects of orally administered medroxyprogesterone acetate.

However, a clinical study of adult women of childbearing potential given medroxyprogesterone acetate IM, 150 mg every 3 months, for contraception, demonstrated an average decrease of 5.4% in lumbar spine BMD over 5 years, with at least partial recovery of this bone loss during the first two years after treatment is discontinued. A similar clinical study of medroxyprogesterone acetate 150 mg IM every 3 months in adolescent females, for contraception, demonstrated similar decreases in BMD, which were also more pronounced during the first two years of treatment and which again were at least partially reversible when treatment was discontinued, Decreases in serum estrogen due to medroxyprogesterone acetate may result in a decrease in bone mineral density (BMD) in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

It is recommended that all patients have adequate calcium and vitamin D intake.

An evaluation of BMD may be appropriate in some patients who use medroxyprogesterone acetate long-term.

Unexpected vaginal bleeding during therapy with medroxyprogesterone acetate should be investigated.
This product can exert adrenocortical effects. Some patients receiving medroxyprogesterone acetate may exhibit suppressed adrenal function. Medroxyprogesterone acetate may decrease ACTH and hydrocortisone blood levels. This should be borne in mind in patient surveillance and regular monitoring instituted during therapy with high doses or over long periods.

Medroxyprogesterone acetate may produce Cushingoid symptoms.

The use of this product in some patients may result in weight gain or fluid retention. As medroxyprogesterone acetate may cause some degree of fluid retention, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.

This product should be used with caution in patients with epilepsy, migraine, asthma, hypertension, cardiac or renal dysfunction.

A decrease in glucose tolerance may occur. Patients with latent or actual diabetes should be kept under careful surveillance.

Acute impairment of vision, onset of migraine, diplopia or proptosis are indications for ophthalmological evaluation for papilloedema or retinal vascular disease. If examination reveals papilledema or retinal vascular lesions, medication should not be re-administered.

Hypercalcaemia may occur in patients with breast cancer.

Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Provera has not been causally associated with the induction of thromboembolic disorders; however any patient who develops this kind of event while undergoing treatment with Provera should have their general medical condition and need for treatment assessed before continuing therapy.

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

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

The results of glucose tolerance and metyrapone tests may be affected by the use of Provera.

Medroxyprogesterone acetate 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.

Pathologists should be informed of the patient's ingestion of Provera if endometrial or endocervical tissue is submitted for examination.

Excipient Information
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 interactions

Aminoglutethimide administered concomitantly with high doses of medroxyprogesterone acetate may significantly depress the serum concentrations of medroxyprogesterone acetate. Users of high-dose medroxyprogesterone acetate should be warned of the possibility of decreased efficacy with the use of aminoglutethimide.

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Medroxyprogesterone acetate 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.
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. There is no definitive information for the other formulations of medroxyprogesterone acetate (see section 5.2).

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.

Progesterone and certain progestogens have been shown to produce reversible virilization in some female offspring of women treated with such substances during pregnancy.

Breast-feeding
Medroxyprogesterone acetate and its metabolites are excreted in breast milk. There is no evidence to suggest that this presents any hazard to the nursing child.

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			Pulmonary embolism			

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)
disorders						
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 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 via HPRA Pharmacovigilance. Website: www.hpra.ie

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 progestogen.

5.2 Pharmacokinetic properties

Medroxyprogesterone acetate is absorbed from the gastro intestinal tract. It is hydroxylated in the liver.

5.3 Preclinical safety data

No further preclinical safety data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Maize starch
Byco C (Hydrolysed gelatine)
Macrogol 400
Sodium starch glycollate (Type A)
Docusate sodium with sodium benzoate (E211)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Amber glass bottles with screw caps or HDPE bottles with tamper evident caps containing 100 tablets.

PVC/Al foil blister strips of 10 tablets, each box containing 3, 6 or 10 strips (30, 60, 100 tablets respectively)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/134/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th March 1994
Date of last renewal: 1st April 2008

10 DATE OF REVISION OF THE TEXT

January 2021