SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

PROVERA® 100 mg

PROVERA® 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA 100 mg: Each tablet contains 100 mg medroxyprogesterone acetate

PROVERA 500 mg: Each tablet contains 500 mg medroxyprogesterone acetate

Preservative: Sodium benzoate 0,07 % m/m

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

PROVERA 100 mg tablets: A white, circular, flat, bevelled tablet marked U467 on one side and scored on the reverse.

PROVERA 500 mg tablets: A white, capsule-shaped tablet embossed Upjohn 717 on one side only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROVERA is indicated in the palliative treatment of:

- Recurrent and/or metastatic endometrial cancer
- Recurrent and/or metastatic renal cancer
- Recurrent and/or metastatic breast cancer in post-menopausal women

4.2 Posology and method of administration

Posology

PROVERA is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced, inoperable cases including those with recurrent or metastatic disease.

For the treatment of endometrial and renal cancer a dosage of 200 mg to 600 mg PROVERA per day is recommended.

For the treatment of breast cancer in post-menopausal women, a dosage of 400 mg to 1 200 mg PROVERA per day is recommended.

Method of administration

For oral use.

4.3 Contraindications

PROVERA is contraindicated in patients with the following conditions:

- Known hypersensitivity to medroxyprogesterone acetate or any of the excipients of PROVERA
- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Severe liver dysfunction

4.4 Special warnings and precautions for use

General

Before using PROVERA, the status of the patient should be carefully evaluated.

Unexpected vaginal bleeding during therapy with PROVERA should be investigated.

PROVERA may cause weight gain and fluid retention. Therefore caution should be exercised in treating any patient with a pre-existing medical condition that may be adversely affected by weight gain or fluid retention.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use and preparations containing estrogen and/or progesterone/progestogen (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Patients with a history of treatment for depression should be carefully monitored while receiving PROVERA therapy. Some patients may complain of premenstrual-like depression while on PROVERA therapy.

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. Diabetic patients should be carefully observed while receiving PROVERA.

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

The medical practitioner/laboratory should be informed that use of PROVERA may decrease the levels of the following endocrine biomarkers:

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

The following laboratory tests may be affected by the use of PROVERA:

- Glucose tolerance test
- Metyrapone test

If there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine PROVERA should not be used, pending examination. If examination reveals papilloedema or retinal vascular lesions, PROVERA should not be used again.

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

Decrease in bone mineral density
Long-term use of PROVERA causes loss of bone mineral density.

Oncology
The high doses of PROVERA used in the treatment of cancer patients may produce cushingoid symptoms, e.g. moon faces, fluid retention, glucose intolerance and blood pressure elevations.

Patients receiving PROVERA may exhibit suppressed adrenal function. PROVERA may decrease ACTH and hydrocortisone blood levels.

The medical practitioner/laboratory should be informed that in addition to the endocrine biomarkers listed above, the use of PROVERA 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.

Breast cancer

The use of combined oral estrogen/progestin by postmenopausal women has been reported to increase the risk of breast cancer. Results from a randomised placebo-controlled trial, the Women's Health Initiative (WHI) trial, and epidemiological studies have reported an increased risk of breast cancer in women taking estrogen/progestin combinations for hormone therapy (HT) for several years. In the WHI conjugated equine estrogens (CEE) plus medroxyprogesterone acetate trial and observational studies, the excess risk increased with duration of use. The use of estrogen plus progestin has also been reported to result in an increase in abnormal mammograms requiring further evaluation.

In several epidemiologic studies no overall increased risk for breast cancer was found among users of injectable depot progestogens in comparison to non-users. However, an increased relative risk (e.g., 2,0 in one study) was found for women who currently used injectable depot progestogens or had used them up to five years before. It is not possible to infer from these data whether this increased rate of breast cancer diagnosis among current users is due to increased surveillance among current users, the biological effects of injectable progestogens, or a combination of reasons.

Cardiovascular disorders

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. Several randomised, prospective trials on the long-term effects of a combined estrogen/progestin regimen in postmenopausal women have reported an increased risk of cardiovascular events such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism.

Coronary artery disease

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous use of combined conjugated estrogen and medroxyprogesterone acetate.

Two large clinical trials [WHI CEE/medroxyprogesterone acetate and Heart and Estrogen/progestin Replacement Study (HERS)] showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit.

In the WHI CEE/medroxyprogesterone acetate trial, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CEE/medroxyprogesterone acetate compared to women receiving placebo (37 vs 30 per 10 000 person years). The increase in VTE risk was observed in year one and persisted over the observation period.

Stroke

In the WHI CEE/medroxyprogesterone acetate trial, an increased risk of stroke was observed in women receiving CEE/medroxyprogesterone acetate compared to women receiving placebo (29 vs 21 per 10 000 person-years). The increase in risk was observed in year one and persisted over the observation period.

Venous thromboembolism/pulmonary embolism

Hormone therapy (HT) such as PROVERA is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. In the WHI CEE/medroxyprogesterone acetate trial, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism was observed in women receiving CEE/medroxyprogesterone acetate compared to women receiving placebo. The increase in risk was observed in year one and persisted over the observation period.

Dementia

The Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, CEE/medroxyprogesterone acetate reported an increased risk of probable dementia in postmenopausal women 65 years of age or older. In addition, CEE/medroxyprogesterone acetate therapy did not prevent mild cognitive impairment (MCI) in these women. Use of hormone therapy (HT) to prevent dementia or MCI in women 65 years or older is not recommended.

Ovarian cancer

Current use of estrogen only or estrogen plus progestin products in post-menopausal women for five or more years, has been associated with an increased risk of ovarian cancer.

History and physical exam recommendation

A complete medical and family history should be taken before the initiation of any hormone therapy. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology.

4.5 Interaction with other medicines and other forms of interaction

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

PROVERA is metabolised *in vitro* primarily by hydroxylation via CYP3A4. Specific interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on PROVERA have not been conducted and therefore the clinical effects of CYP3A4 inducers or inhibitors are unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy

PROVERA is contraindicated in women who are pregnant (see section 4.3).

Reports suggest an association between intra-uterine exposure to progestational medicines in the first trimester of pregnancy and genital abnormalities in foetuses.

If the patient becomes pregnant while using PROVERA, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

PROVERA and its metabolites are excreted in breast milk. Mothers on PROVERA therapy should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

The effect of PROVERA on the ability to drive and use machinery has not been systematically evaluated. Side effects of PROVERA that may affect driving and use of machinery are e.g., dizziness, tremors, loss of concentration, retinal embolism and euphoria (see section 4.8). Patients should determine how they are affected before engaging in such activities.

4.8 Undesirable effects

The table below provides a listing of adverse medicine reactions with frequencies based on all-causality data from 1 337 patients who received PROVERA in 4 pivotal studies that evaluated efficacy and safety of PROVERA for oncology indications.

Frequencies are defined as:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to <1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

System organ class	Frequency	Side effect
Immune system disorders	Uncommon	Angioedema
	Rare	Medicine hypersensitivity
	Not known	Anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Uncommon	Corticoid-like effects
	Not known	Prolonged anovulation

Metabolism and nutrition disorders	Common	Increased weight, increased appetite
	Uncommon	Exacerbated diabetes mellitus, hypercalcaemia
Psychiatric disorders	Common	Insomnia
	Uncommon	Depression, euphoria, decreased libido
	Rare	Nervousness
	Not known	Confusion
Nervous system disorders	Common	Headache, dizziness, tremors
	Rare	Cerebral infarction, somnolence
	Not known	Loss of concentration, adrenergic-like effects
Eye disorders	Not known	Retinal embolism and thrombosis, diabetic cataract, visual impairment
Cardiac disorders	Uncommon	Congestive cardiac failure
	Rare	Myocardial infarction
	Not known	Tachycardia, palpitations
Vascular disorders	Uncommon	Thrombophlebitis
	Rare	Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary embolism
Gastrointestinal disorders	Common	Vomiting, constipation, nausea
	Uncommon	Diarrhoea, dry mouth
Hepato-biliary disorders	Rare	Jaundice
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Acne, hirsutism
	Rare	Alopecia, rash
	Not known	Urticaria, pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms

Renal and urinary disorders	Not known	Glycosuria
Reproductive system and breast disorders	Common	Erectile dysfunction
	Uncommon	Dysfunctional uterine bleeding (irregular, increased, decreased, spotting), breast pain
	Not known	Amenorrhoea, uterine cervical erosions, cervical discharge, galactorrhoea
General disorders and administration site conditions	Common	Oedema/fluid retention, fatigue
	Rare	Malaise, pyrexia
Investigations	Rare	Decreased glucose tolerance, increased blood pressure
	Not known	Abnormal liver function test, increased white blood cell count, increased platelet count

The side effects below were reported during post-marketing experience

System organ class	**Side effect**
Metabolism and nutrition disorders	Moon faces
Psychiatric disorders	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide
Skin and subcutaneous tissue disorders	Acquired lipodystrophy
Reproductive system and breast disorders	Breast tenderness

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Patients receiving pharmacological doses of PROVERA for the treatment of neoplasms (400 mg/day or greater) may exhibit effects resembling those of corticoid excess.

Observation only is recommended for management, although it may be necessary to consider dose reduction. No symptoms of acute overdosage have been observed. Overdose treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterone without estrogens

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

Mechanism of action

Medroxyprogesterone acetate 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 follicle stimulating hormone (FSH) and luteinising hormone (LH)
- Decrease of adrenocorticotropic hormone (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 antitumour activity. When medroxyprogesterone acetate is given to patients at high doses (either by the oral route or by IM injection) it is effective in the palliative treatment of hormone-responsive malignant neoplasms.

5.2 Pharmacokinetic properties

Absorption

After oral intake, medroxyprogesterone acetate maximum concentrations are obtained between 2 to 4 hours. The elimination half-life of oral medroxyprogesterone acetate is approximately 17 hours. It is 90 % protein bound, and is mainly excreted in the urine.

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

Distribution

Medroxyprogesterone acetate is approximately 90 % protein bound, primarily to albumin; no medroxyprogesterone acetate binding occurs with sex hormone-binding globulin.

Biotransformation

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

Elimination

Most medroxyprogesterone acetate metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulphates. Mean percent dose excreted in the 24-hour urine of patients with fatty liver as intact medroxyprogesterone acetate after a 10 mg or 100 mg dose was 7,3 % and 6,4 %, respectively. Elimination half-life of oral medroxyprogesterone acetate is 12 to 17 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch
Docusate sodium
Gelatine
Magnesium stearate
Microcrystalline cellulose
Polyethylene glycol
Sodium benzoate
Sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years when stored in blisters.

6.4 Special precautions for storage

Store at room temperature between 15 and 30 °C.
Protect from light.

6.5 Nature and contents of container

PROVERA 100 mg tablets are available in blister packs of 100 tablets.

PROVERA 500 mg tablets are available in blisters of 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

PROVERA 100 mg tablets: S/21.8.2/1

PROVERA 500 mg tablets: W/21.8.2/462

9. DATE OF FIRST AUTHORISATION

PROVERA 100 mg: 13 Jan 1989

PROVERA 500 mg: 29 Dec 1989

10. DATE OF REVISION OF THE TEXT

25 January 2023

BOTSWANA: S2

Provera 100 mg – Reg. No.: B9312125

NAMBIA: S2

Provera 100 mg – Reg. No.: 90/21.8.2/001350

Provera 500 mg – Reg. No.: 90/21.8.2/001351