SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PROVERA® 5

PROVERA® 10

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVERA 5: Each tablet contains 5 mg medroxyprogesterone acetate.

PROVERA 10: Each tablet contains 10 mg medroxyprogesterone acetate.

Contains sugar (lactose monohydrate and sucrose).

Excipients with known effect

PROVERA 5: Each tablet contains 84,2 mg lactose monohydrate and 1,47 mg sucrose.

PROVERA 10: Each tablet contains 110 mg lactose monohydrate and 2,0 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

PROVERA 5: Light blue, round tablets. One surface is engraved with the logo “286” on both sides of a break score. The other surface is engraved with the logo “U”.

PROVERA 10: A white, round, semi-oval, convex tablet, scored on one side and marked “Upjohn 50” on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Dysfunctional uterine bleeding

- Mild to moderate endometriosis
- To oppose the endometrial effects of estrogen in menopausal women treated with estrogen
- Alleviation of menopausal vasomotor symptoms
- Diagnostic uses:
  - Primary amenorrhoea
  - Secondary amenorrhoea

4.2 Posology and method of administration

Posology

Dysfunctional uterine bleeding

In dysfunctional uterine bleeding PROVERA may be given in doses ranging from 5 mg to 10 mg for 5 to 10 days beginning on the assumed or calculated 16th to 21st day of the cycle.

When bleeding is due to a deficiency of both ovarian hormones, as indicated by a poorly developed proliferative endometrium, estrogens should be used in conjunction with PROVERA. If bleeding is controlled satisfactorily, two subsequent cycles of treatment should be given.

Endometriosis

Beginning on the first day of the menstrual cycle, 10 mg of PROVERA may be given three times a day for 90 consecutive days.

To oppose the endometrial effects of estrogen in estrogen-treated post-menopausal women

5 mg to 10 mg PROVERA per day for at least 10 days beginning on the 16th day of a 25 day course of estrogen therapy. Progestin withdrawal bleeding should occur, beginning on the 3rd to 7th day post PROVERA treatment.

Menopause

10 mg to 20 mg PROVERA per day given continuously.

Primary and secondary amenorrhoea

5 mg to 10 mg PROVERA per day for 10 days. Progestin withdrawal bleeding should ensue within 3 - 7 days if the endometrium has been previously primed with adequate endogenous estrogen. Pregnancy must be excluded before administration of PROVERA.

Method of administration

For oral use.

4.3 Contraindications

PROVERA is contraindicated in patients with the following conditions

- Known hypersensitivity to medroxyprogesterone acetate or to any of the excipients of PROVERA (listed in section 6.1)
- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
- Liver dysfunction or disease
- Known or suspected malignancy of breast or genital organs
- Undiagnosed vaginal bleeding
- Missed or incomplete abortion
- Known or suspected pregnancy

4.4 Special warnings and precautions for use

General

Unexpected vaginal bleeding during therapy with PROVERA should be investigated.

PROVERA induces withdrawal bleeding in amenorrhoeic anovulatory women. It also produces secretory changes and a luteal type of vaginal smear in anovulatory patients with adequate estrogens. Breakthrough bleeding is likely to occur in patients treated for endometriosis.

PROVERA may cause fluid retention, therefore, caution should be exercised in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention such as epilepsy, migraine, asthma, cardiac or renal dysfunction.

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 who have a history of treatment for depression should be carefully monitored while receiving PROVERA and PROVERA discontinued if the depression recurs to a serious degree.

Patients receiving PROVERA may exhibit a decreased glucose tolerance. 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 results may be altered by the use of estrogen progestin combination medicines:

- Gonadotropin levels
- Plasma progesterone levels
- Urinary pregnanediol levels
- Plasma estrogen levels
- Plasma cortisol levels
- Glucose tolerance test
- Metyrapone test: pregnanediol determination

- Increased sulfobromophthalein and other hepatic function tests
- Coagulation tests: increase in prothrombin factors VII, VIII, IX and X
- Thyroid function: increase in PBI and butanol extractable protein bound iodine and decrease in T3 uptake values

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 re-used.

The medical practitioner should be alert to the earliest manifestations of thrombotic or thromboembolic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis), however PROVERA is not recommended in any patient with a history of venous thromboembolism (VTE). Should any of these occur or be suspected, PROVERA should be discontinued immediately.

PROVERA may mask the onset of the climacterium.

PROVERA may decrease bone mineral density.

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 only a

few 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

HT 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.

Lactose

PROVERA contains lactose. Patients with ~~the~~ rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sucrose

PROVERA contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Aminoglutethimide administered concomitantly with PROVERA may significantly depress the serum concentrations of PROVERA.

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).

Cases of clitoral hypertrophy have been reported in newborn females~~,~~ whose mothers received PROVERA during pregnancy. Prolonged postpartum bleeding, post-abortal bleeding and missed abortion have been reported. Female foetal masculinisation has been observed in infants born from mothers receiving progestins.

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. PROVERA should not be given to women breastfeeding 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.

4.8 Undesirable effects

The table below provides a listing of adverse medicine reactions with frequencies based on all-causality data from Phase 3 clinical studies that evaluated efficacy and safety of PROVERA in gynaecology. The most frequently (> 5 %) reported adverse drug reactions were dysfunctional uterine bleeding (19 %), headache (12 %) and nausea (10 %).

Frequencies are defined as:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, <1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000)

System organ class	**Frequency**	**Side effects**
Immune system disorders	Common	Medicine hypersensitivity
	Not known	Anaphylactic reaction, anaphylactoid reaction, angioedema
Endocrine disorders	Not known	Prolonged anovulation
Psychiatric disorders	Common	Depression, insomnia, nervousness
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Not known	Somnolence
Vascular disorders	Not known	Venous thrombo-embolism
Gastrointestinal disorders	Very common	Nausea
Hepato-biliary disorders	Not known	Jaundice, cholestatic jaundice
Skin and subcutaneous tissue disorders	Common	Alopecia, acne, urticaria, pruritus
	Uncommon	Hirsutism
	Not known	Rash
Reproductive system and breast disorders	Very common	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting)
	Common	Cervical discharge, breast pain, breast tenderness
	Uncommon	Galactorrhoea
	Not known	Amenorrhoea, uterine cervical erosion
General disorders and administration site conditions	Common	Pyrexia, fatigue
	Uncommon	Oedema, fluid retention
Investigations	Common	Increased weight
	Not known	Decreased glucose tolerance, decreased weight

The below side effects 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
Eye disorders	Neuro-ocular lesions, e.g. retinal thrombosis and optic neuritis
Hepato-biliary disorders	Neonatal jaundice
Skin and subcutaneous tissue disorders	Melasma or chloasma, acquired lipodystrophy

The following adverse reactions have been observed in patients receiving estrogen progestin combination medicines. In view of these observations, patients on progestin therapy should be carefully observed.

System organ class	Side effect
Metabolism and nutrition disorders	Changes in appetite
Psychiatric disorders	Changes in libido
Skin and subcutaneous tissue disorders	Erythema nodosum, erythema multiforme, haemorrhagic eruption
Musculoskeletal and connective tissue disorders	Backache
Renal and urinary disorders	Cystitis-like syndrome
Reproductive system and breast disorders	Premenstrual-like syndrome
Investigations	Rise in blood pressure

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

Treatment should be 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)

Medroxyprogesterone acetate, administered to women with adequate endogenous estrogen transforms proliferative into secretory endometrium.

5.2 Pharmacokinetic properties

Absorption

After oral administration of medroxyprogesterone acetate maximum concentration is obtained between 2 to 4 hours. The 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 however no dosage adjustment is recommended. 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

Calcium stearate

Lactose monohydrate

Liquid paraffin

Maize starch

Sucrose

Talc

PROVERA 5 mg tablets contain a colourant (FD & C Blue No. 2 Aluminium Lake colour mixture CI: 73015).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Provera 5: 60 months in blisters.

Provera 10: 36 months in blisters.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

6.5 Nature and contents of container

PROVERA 5 mg tablets are available in blister packs of 30 and 100 tablets.

PROVERA 10 mg tablets are available in blister packs 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 5: G2988 (Act/101/1965)

PROVERA 10: Z/21.8.2/363

9. DATE OF FIRST AUTHORISATION

PROVERA 5: Not applicable (Old medicine)

PROVERA 10: 24 November 1993

10. DATE OF REVISION OF THE TEXT

20 October 2022

BOTSWANA: S2

PROVERA 5 mg: Reg. No.: B9312120

PROVERA 10 mg: Reg. No. B9312130

NAMIBIA: S2

PROVERA 5 mg: Reg. No.: 14/21.8/0438

PROVERA 10 mg: Reg. No.: 04/21.8.2/0740