SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DEPO-PROVERA® 150 injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains medroxyprogesterone acetate 150 mg.

Sugar free.

Excipients with known effect

Preservatives

Methyl parahydroxybenzoate 0,14 % m/v

Propyl parahydroxybenzoate 0,015 % m/v

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection

White to off-white injectable suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Endometriosis
- Contraception (ovulation suppression)
- Endometrial cancer: As adjunctive and/or palliative therapy in inoperable, recurrent or metastatic endometrial carcinoma
- Renal cancer: As adjunctive and/or palliative therapy in recurrent and/or metastatic adenocarcinoma of the kidney

4.2 Posology and method of administration

Posology

Endometriosis

The recommended dose of DEPO-PROVERA in this condition is 50 mg weekly or 100 mg every 2 weeks intramuscularly for at least 6 months. It should be noted that return of ovulation may be delayed following this therapy due to the depot properties of the medicine (see section 4.4).

Contraception

The recommended dose is 150 mg DEPO-PROVERA every three months administered by deep intramuscular injection. To increase assurance that the patient is not pregnant at the time of the first administration, it is recommended that this injection be given during the first 5 days after the onset of a normal menstrual period, within 5 days postpartum if not breastfeeding, or, if exclusively breastfeeding, at or after the sixth week postpartum. If the period between injections is greater than 14 weeks, the medical practitioner should determine that the patient is not pregnant before administering DEPO-PROVERA.

Switching from other methods of contraception

When switching from other contraceptive methods, DEPO-PROVERA should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of DEPO-PROVERA within 7 days after taking their last active pill).

Endometrial and renal carcinoma

Doses of 400 mg to 1000 mg of DEPO-PROVERA intramuscularly per week are recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilised, it may be possible to maintain improvement with as little as 400 mg per month.

Special populations

Hepatic insufficiency

No clinical studies have evaluated the effect of hepatic disease on the pharmacokinetics of DEPO-PROVERA. However, DEPO-PROVERA is almost exclusively eliminated by hepatic metabolism and steroid hormones may be poorly metabolised in patients with severe liver insufficiency (see section 4.3).

Renal insufficiency

No clinical studies have evaluated the effect of renal disease on the pharmacokinetics of DEPO-PROVERA. However, since DEPO-PROVERA is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

Paediatric population

DEPO-PROVERA is not indicated before menarche. Data are available in adolescent females (12 to 18 years) (see section 4.4). Other than concerns about loss of bone mineral density (BMD), the safety and effectiveness of DEPO-PROVERA are expected to be the same for post-menarcheal adolescent and adult females.

Method of administration

For intramuscular injection.

The sterile aqueous suspension of DEPO-PROVERA should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension of DEPO-PROVERA.

4.3 Contraindications

- Known hypersensitivity to medroxyprogesterone acetate or to any of the excipients of DEPO-PROVERA (listed in section 6.1)
- Undiagnosed vaginal bleeding
- Undiagnosed urinary tract bleeding
- Undiagnosed breast pathology
- Thrombophlebitis, or a history of thrombophlebitis
- Severe impairment of liver function
- Known or suspected pregnancy (see section 4.6)
- Known or suspected malignancy of the breast (excluding use in oncology indications)

- Depression not well controlled with treatment
- A history of depression with the use of hormonal contraceptives

4.4 Special warnings and precautions for use

Contraception and endometriosis

Loss of bone mineral density (BMD)

Use of DEPO-PROVERA reduces serum estrogen levels and is associated with statistically significant loss of BMD as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of DEPO-PROVERA by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adult and adolescent females, the decrease in BMD appears to be at least partially reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases.

Medical examinations

Assessment of women prior to starting hormonal contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include a measurement of blood pressure and, if judged appropriate by the medical practitioner, breast, abdominal and pelvic examination including cervical cytology.

Other birth control methods should be considered when DEPO-PROVERA injection is required as a long-term birth control method (e.g., longer than 2 years).

BMD should be evaluated when a female needs to continue to use DEPO-PROVERA long-term. In adolescent females, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods or endometrial treatments should be considered in the risk/benefit analysis for the use of DEPO-PROVERA in woman with osteoporotic risk factors. DEPO-PROVERA can pose an additional risk in patients with risk factors for osteoporosis (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, low body mass index or eating disorder, e.g. anorexia nervosa or bulimia, strong family history of osteoporosis or chronic use of medicines that can reduce bone mass such as anticonvulsants or corticosteroids).

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

BMD changes in adult women

In a controlled, clinical study, adult woman using DEPO-PROVERA for up to 5 years for contraception showed spine and hip mean BMD decreases of 5 - 6 %, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of –2,86 %, -4,11 %, -4,89 %, -4,93 % and –5,38 % after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of DEPO-PROVERA, there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. BMD increased but deficits at the total hip, femoral neck and lumbar spine remained. A longer duration of treatment was associated with a slower rate of BMD recovery.

Since loss of BMD may occur in pre-menopausal women who use DEPO-PROVERA long-term, a risk/benefit assessment which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be considered.

Endometrial and renal carcinoma (high dose parenteral formulations)

Decrease in bone mineral density

There are no studies on the BMD effects of high doses of DEPO-PROVERA.

Decreases in serum estrogen due to DEPO-PROVERA may result in a decrease in BMD in a pre-menopausal woman and may increase her risk for developing osteoporosis later in life.

Thromboembolic disorders

Any patient who develops signs and/or symptoms consistent with a thromboembolic disorder while undergoing therapy with DEPO-PROVERA should have her status and need for treatment carefully assessed before continuing therapy.

Ocular disorders

In any patient who develops an acute impairment of vision, proptosis, diplopia, or migraine headache, DEPO-PROVERA should be discontinued and the patient carefully evaluated ophthalmologically to exclude the presence of papilloedema or retinal vascular lesions before continuing treatment.

Anaphylactic and anaphylactoid reactions

Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with DEPO-PROVERA.

Bleeding irregularities

Most women receiving DEPO-PROVERA for contraception experience disruption of menstrual bleeding patterns. It is recommended that medical practitioners or others directly responsible for patients using DEPO-PROVERA advise them at the beginning of treatment that their menstrual cycle may be disrupted, that irregular and unpredictable bleeding, spotting or heavy or continuous bleeding may occur, but that this usually decreases to the point of amenorrhoea as treatment with DEPO-PROVERA continues, without other therapy being required.

Restoration of normal menstrual cycling may take from 5 to 28 months after the last injection of DEPO-PROVERA.

In cases of abnormal bleeding, appropriate investigation should first be instituted to rule out the possibility of organic pathology before continuing treatment with DEPO-PROVERA**.**

In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, organic causes should be excluded. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Following repeated injections, amenorrhoea and anovulation may persist for periods up to 18 months and, in rare instances, for longer periods.

The use of DEPO-PROVERA may mask the onset of the climacteric.

Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, DEPO-PROVERA is not recommended for treatment of secondary amenorrhoea or dysfunctional uterine bleeding.

Central nervous system disorders

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 mental depression should be carefully observed and DEPO-PROVERA discontinued if the depression recurs to a serious degree. Some patients may complain of premenstrual-like depression while on DEPO-PROVERA therapy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in patients on progestogens including DEPO-PROVERA. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving DEPO-PROVERA therapy.

Liver function

Certain endocrine and possibly liver function tests may be affected by treatment with DEPO-PROVERA. Therefore, if such tests are abnormal in a patient taking DEPO-PROVERA, it is recommended that they be repeated after the medicine has been withdrawn. If jaundice develops, consideration should be given to not re-administer DEPO-PROVERA.

Weight changes

Weight gain may be associated with use of DEPO-PROVERA.

Effects on laboratory tests

The pathologist should be advised of DEPO-PROVERA therapy when relevant specimens are submitted.

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

- gonadotropin levels
- plasma progesterone levels
- urinary pregnanediol levels
- plasma testosterone levels (in the male)
- plasma estrogen levels (in the female)
- plasma cortisol levels
- glucose tolerance test
- metyrapone test
    - The medical practitioner/laboratory should be informed that, in addition to the endocrine biomarkers listed above, the use of DEPO-PROVERA in oncology indications (endometrial and renal carcinoma) may also cause partial adrenal insufficiency (decrease in pituitary-adrenal axis response) during metyrapone testing. Thus, the ability of adrenal cortex to respond to adrenocorticotropic hormone (ACTH) should be demonstrated before metyrapone is administered.
- hypercalcaemia
- sex hormone-binding-globulin

Fluid retention

Because DEPO-PROVERA may cause fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

Adrenocortical effects

Clinical suppression of adrenocortical function has not been observed at the dose levels employed for contraception. However, at very high doses (500 mg daily or more) used in the treatment of certain cancers, corticoid-like activity has been reported.

Some patients receiving DEPO-PROVERA may exhibit suppressed adrenal function. DEPO-PROVERA may decrease ACTH and hydrocortisone blood levels.

The high dose of DEPO-PROVERA used in the treatment of cancer patients may, in some cases produce Cushingoid symptoms, e.g. moon faces, fluid retention, glucose intolerance, and blood pressure elevation.

Cancer risks

Long-term case-controlled surveillance of users of DEPO-PROVERA found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer.

Sexually transmitted infections

Patients should be counselled that DEPO-PROVERA does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) or other sexually transmitted diseases but equally, DEPO-PROVERA is a sterile injection and, used as directed, will not expose them to sexually transmitted infections. Safer sex practices including correct and consistent use of condoms reduce the transmission of STIs through sexual contact, including HIV.

Paediatric population

BMD changes in adolescent females (12 – 18 years)

An open-label clinical study of DEPO-PROVERA (150 mg IM every 12 weeks for 240 weeks) in adolescent females (12 – 18 years) for contraception showed that DEPO-PROVERA was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 2,1 % after 240 weeks; mean decreases for the total hip and femoral neck were 6,4 % and 5,4 % respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. In adolescent females, the decrease in BMD appears to be fully reversible after DEPO-PROVERA is discontinued and ovarian estrogen production increases. Full recovery took 1,2 years at the lumbar spine, 4,6 years at the total hip and 4,6 years at the femoral neck after discontinuation of treatment.

Preservative sensitivity

DEPO-PROVERA contains the excipients methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

4.5 Interaction with other medicines and other forms of interaction

Aminoglutethimide administered concomitantly with DEPO-PROVERA may significantly depress the bioavailability of DEPO-PROVERA**.**

DEPO-PROVERA is metabolised *in vitro* primarily by hydroxylation via cytochrome P450 3A4. Specific interaction studies evaluating the clinical effects of cytochrome P450 3A4 inhibitors or inducers on DEPO-PROVERA have not been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of DEPO-PROVERA during pregnancy is contraindicated (see section 4.3). DEPO-PROVERA should not be used as a diagnostic test for pregnancy.

Some reports suggest an association between intra-uterine exposure to progestational medicines, including DEPO-PROVERA, 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 with DEPO-PROVERA 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 DEPO-PROVERA are uncommon.

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

Breastfeeding

DEPO-PROVERA and its metabolites are excreted in breast milk but 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

The effect of DEPO-PROVERA on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Adverse events have been categorised as follows:

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); not known (cannot be estimated from the available data).

Contraception

A clinical trial conducted using DEPO-PROVERA for contraception in women who were treated for up to 7 years reported the adverse reactions in the table below. The following adverse reactions were reported by more than 5 % of patients: abdominal pain or discomfort, dizziness, weight fluctuation, nervousness and headache.

System Organ Class	**Frequency**	**Undesirable effects**
Immune system disorders	Uncommon	Medicine hypersensitivity
	Rare	Anaphylactic reaction, anaphylactoid reaction, angioedema
Endocrine disorders	Rare	Prolonged anovulation

Psychiatric disorders	Very common	Nervousness
	Common	Decreased libido, anorgasmia, depression, insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Seizure, somnolence
Vascular disorders	Common	Hot flushes
	Rare	Thromboembolic disorders (thrombosis, embolism, thrombophlebitis and pulmonary embolism)
Gastrointestinal disorders	Very common	Abdominal pain, abdominal discomfort
	Common	Abdominal distension, nausea
	Uncommon	Diarrhoea
Hepato-biliary disorders	Uncommon	Jaundice, liver disorder
Skin and subcutaneous tissue disorders	Common	Rash, acne, alopecia
	Uncommon	Hirsutism, pruritis, urticaria
Musculoskeletal and connective tissue disorders	Common	Back pain, leg cramps
	Rare	Muscle cramps, arthralgia, muscle spasms
Reproductive system and breast disorders	Very common	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), amenorrhoea
	Common	Vaginal discharge, breast pain, breast tenderness, dysmenorrhoea, pelvic pain, vaginitis
	Uncommon	Galactorrhoea
	Rare	Cervix changes in erosion and secretion, virilisation, feminisation
	Very common	Fluid retention

General disorders and administration site conditions	Common	Asthenia, fatigue
	Rare	Pyrexia
	Very rare	Injection-site reactions (pain, residual lumps and change in skin colour at site of injection)
Investigations	Very common	Weight change
	Rare	Decreased glucose tolerance, loss of bone mineral density

Contraception post-marketing reported side effects

The following side effects have been reported with the post-marketing use of hormonal contraceptives:

System Organ Class	**Undesirable effects**
Psychiatric disorders	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide
Skin and subcutaneous tissue disorders	Acquired lipodystrophy
Musculoskeletal and connective tissue disorders	Osteoporosis including osteoporotic fractures
General disorders and administration site conditions	Injection site nodule/lump, injection site persistent atrophy/indentation/dimpling, injection site reaction, injection site pain/tenderness

Oncology

System Organ Class	**Frequency**	**Undesirable effects**
Endocrine disorders	Uncommon	Moon face
Metabolism and nutrition disorders	Common	Weight increase

Nervous system disorders	Common	Tremor
Vascular disorders	Uncommon	Thrombophlebitis
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Not known	Osteoporosis including osteoporotic fractures
Reproductive system and breast disorders	Uncommon	Dysfunctional vaginal bleeding (irregular, increased, decreased, spotting)
General disorders and administration site conditions	Common	Oedema/fluid retention
	Rare	Pyrexia
Investigations	Not known	Abnormal liver values

Oncology post-marketing reported side effects

System Organ Class	**Undesirable effects**
Psychiatric disorders	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide
Skin and subcutaneous tissue disorders	Acquired lipodystrophy
General disorders and administration site conditions	Injection site reaction, injection site pain/tenderness, injection site persistent atrophy/indentation/dimpling, injection site nodule/lump

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Nausea, vomiting, somnolence, lower abdominal discomfort, insomnia, fullness and tenderness of the breasts and headache have been attributed to therapeutic doses. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterone with or without estrogens

Medroxyprogesterone acetate has progestational effects. It suppresses the secretion of pituitary gonadotropins which, in turn, prevents follicular maturation, producing long-term anovulation in the reproductive woman. Medroxyprogesterone acetate suppresses the Leydig cell function in the male, i.e. suppresses endogenous testosterone production. A single dose of 50 mg of parenteral medroxyprogesterone acetate has the equivalent effect of 20 mg of parenteral progesterone given daily for 10 days in producing an optimal secretory change in an estrogen-primed endometrium. This steroid also produces typical progestational changes in the cervical mucous (inhibits ferning), increases the viscosity of cervical mucous, thereby increasing the difficulty of sperm penetration; and increases the intermediate cell count in the maturation index of the vaginal epithelium.

The anti-cancer activity of medroxyprogesterone acetate at high doses is unexplained and may be dependent on its effect on the hypothalamic/pituitary/gonadal axis, estrogen receptors or the metabolism of steroids at the tissue level. At the high dose levels used in the treatment of certain cancers, corticoid-like activity may be manifested.

5.2 Pharmacokinetic properties

Absorption

Parenteral medroxyprogesterone acetate is a long-acting progestational steroid. The 100 mg/mL formulation reaches half its initial concentration in about 27 days. Its long duration of action results from its slow absorption from the injection site.

Biotransformation

Medroxyprogesterone acetate is metabolised in the liver. The principal metabolite of medroxyprogesterone acetate that has been identified is a 6α-methyl-6ß,17α,21-trihydroxy-4-pregnene-3,20-dione-17-acetate, which is excreted in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

Macrogol 3350

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

- Store at or below 30 °C
- Do not refrigerate or freeze
- Store vial upright

6.5 Nature and contents of container

DEPO-PROVERA 150 is available as a single dose 2 mL vial or as packs of 25 single dose 2 mL vials.

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 NUMBER

DEPO-PROVERA 150**:** E/21.8.2/114

9. DATE OF FIRST AUTHORISATION

08 February 1973

10. DATE OF REVISION OF THE TEXT

21 September 2022

BOTSWANA: S2

Reg. No.: B9312010

NAMIBIA: S2

Reg. No.: 90/21.8.2/001309

ZIMBABWE: PP

Reg. No.: 72/21.2.3/63