SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

DEPO-PROVERA® 150 (Injection)

COMPOSITION:

Each ml contains:

Medroxyprogesterone Acetate	150 mg
Preservatives:	Methylparaben 0,14 % m/v
	Propylparaben 0,015 % m/v

PHARMACOLOGICAL CLASSIFICATION:

A 21.8.2 Progesterone with or without oestrogens

PHARMACOLOGICAL ACTION:

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 oestrogen-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, oestrogen

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.

PHARMACOKINETIC PROPERTIES:

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.

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.

INDICATIONS:

1. Endometriosis
2. Contraception (ovulation suppression)
3. Endometrial Cancer: As adjunctive and/or palliative therapy in inoperable, recurrent or metastatic endometrial carcinoma.
4. Renal Cancer: As adjunctive and/or palliative therapy in recurrent and/or metastatic adenocarcinoma of the kidney.

CONTRAINDICATIONS:

1. Known sensitivity to medroxyprogesterone acetate.
2. Undiagnosed vaginal bleeding.
3. Undiagnosed urinary tract bleeding.
4. Undiagnosed breast pathology.
5. Thrombophlebitis, or a history of thrombophlebitis.
6. Severe impairment of liver function

WARNINGS AND SPECIAL PRECAUTIONS:

1. **CONTRACEPTION/ENDOMETRIOSIS:**

Loss of Bone Mineral Density (BMD):

Use of **DEPO-PROVERA** reduces serum oestrogen levels and is associated with significant loss of Bone Mineral Density (BMD) as bone metabolism accommodates to a lower oestrogen 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 oestrogen production increases. The degree of reversibility of BMD in adolescent females is unknown.

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, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs 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. A longer duration of treatment was associated with a slower rate of BMD recovery.

Since loss of Bone Mineral Density (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.

BMD Changes in Adolescent Females (12 – 18 years):

Preliminary results from an ongoing, open-label clinical study of **DEPO-PROVERA** (150 mg IM every 12 weeks for up to 5 years) in adolescent females (12 – 18 years) for contraception also showed that **DEPO-PROVERA** was associated with a significant decline in BMD from baseline. The mean decrease in lumbar spine BMD was 4,2 % after 5 years; mean decreases for the total hip and femoral neck were 6.9 % and 6,1 % respectively. In contrast, most adolescent girls will significantly increase bone density during this period of growth following menarche. Preliminary data from a small number of adolescents have shown partial recovery of BMD during the 2-year follow-up period.

2. **ENDOMETRIAL AND RENAL CARCINOMA (High Dose Parenteral Formulations): Decrease in Bone Mineral Density:**

   There are no studies on the bone mineral density (BMD) effects of high doses of parenteral medroxyprogesterone acetate.

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

3. 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.

4. 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 medication.

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

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

7. 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.
8. Some patients receiving **DEPO-PROVERA** may exhibit suppressed adrenal function. Medroxyprogesterone acetate may decrease ACTH and hydrocortisone blood levels.
9. It is recommended that physicians or others directly responsible for these patients advise them at the beginning of treatment that their menstrual cycle may be disrupted, that irregular and unpredictable bleeding or spotting are produced, 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.**
10. All patients should be physically examined before treatment with special reference to breast and pelvic organs as well as a Papanicolaou smear.
11. 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.
12. Patients who have a history of mental depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Some patients may complain of premenstrual-like depression while on **DEPO- PROVERA** therapy.
13. A decrease in glucose tolerance has been observed in patients on progestogens. The mechanisms of this decrease is obscure. For this reason diabetic patients should be carefully observed while receiving progestogen therapy.

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

15. 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 drug has been withdrawn.

16. 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.

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

18. The pathologist should be advised of progestogen therapy when relevant specimens are submitted.

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

    a. Gonadotropin levels

    b. Plasma progesterone levels

    c. Urinary pregnanediol levels

    d. Plasma testosterone levels (in the male)

    e. Plasma oestrogen levels (in the female)

    f. Plasma cortisol levels

    g. Glucose tolerance test

    h. Metyrapone test

20. The physician/laboratory should be informed that in addition to the endocrine biomarkers listed in point 12 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 ACTH should be demonstrated before metyrapone is administered.

21. Hypercalcaemia

22. Because progestogens may cause fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
23. 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.
24. 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.
25. If jaundice develops, consideration should be given to not re-administer the drug.
26. Patients should be counselled that **DEPO-PROVERA** does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

INTERACTIONS:

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

PREGNANCY AND LACTATION:

The use of progestational agents during pregnancy is not recommended. Progestational agents are not recommended as a diagnostic test for pregnancy.

Some reports suggest an association between intra-uterine 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 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.

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

DOSAGE AND DIRECTIONS FOR USE:

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**.

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 **WARNINGS AND SPECIAL PRECAUTIONS**).

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.

USE IN CHILDREN:

DEPO-PROVERA is not indicated before menarche.

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 stabilized, it may be possible to maintain improvement with as little as 400 mg per month.

SIDE EFFECTS:

The following events have been associated with the use of progestogens:

Adverse events have been categorised as follows:

Very common: ≥ 1/10 (≥10 %)

Common: ≥ 1/100 and < 1/10 (≥1 % and <10 %)

Uncommon: ≥ 1/1 000 and < 1/100 (≥0,1 % and <1 %)

Rare: ≥ 1/10 000 and < 1/1 000 (≥0,01 % and <0,1 %)

Very Rare: < 1/10 000 (<0,01 %)

MeDRA System Organ Class	**Frequency**	**Undesirable Effects**
Endocrine disorders	Very rare	Prolonged anovulation, vaginitis
Metabolism and nutrition disorders	Very common	Fluid retention
	Rare	Moon face
Psychiatric disorders	Common	Decreased libido or anorgasmia, depression, insomnia

Nervous system disorders	Very common	Headache, nervousness
	Common	Dizziness
	Uncommon	Convulsions, somnolence
Vascular disorders	Common	Hot flushes
	Very rare	Thromboembolic disorders (thrombophlebitis and pulmonary embolism)
Gastrointestinal disorders	Very common	Abdominal pain or discomfort
	Common	Bloating, nausea
	Uncommon	Diarrhoea
Hepato-biliary disorders	Uncommon	Jaundice
	Very rare	Disturbed liver function
Skin and subcutaneous tissue disorders	Common	Rash, acne, alopecia
	Uncommon	Hirsutism, pruritis, urticaria
	Very rare	Hypersensitivity reactions (e.g., anaphylaxis & anaphylactoid reactions, angio-oedema)
Musculoskeletal and connective tissue disorders	Common	Backache
	Rare	Muscle cramps, osteoporosis and related fractures
	Very rare	Arthralgia, leg cramps

Reproductive system and breast disorders	Very common	Abnormal uterine bleeding (irregular, increase, decrease), amenorrhoea
	Common	Leucorrhoea, mastodynia, breast tenderness, dysmenorrhoea
	Uncommon	Galactorrhoea
	Rare	Cervix: changes in erosion and secretion; virilisation, feminisation
	Very rare	Pelvic pain
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
	Very rare	Decreased glucose tolerance, loss of Bone Mineral Density

Additional Adverse Events Reported During Post-Marketing Experience:

In post-marketing experience, there have been rare cases of osteoporosis including osteoporotic fractures reported in patients taking **DEPO-PROVERA.**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

IDENTIFICATION:

White to off-white injectable suspension.

PRESENTATION:

DEPO-PROVERA 150 is available as a single dose 1 ml vial or as packs of 25 single dose 1 ml vials.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Do not refrigerate or freeze.

Store vial upright.

Keep out of reach of children.

REGISTRATION NUMBER:

DEPO-PROVERA 150: E/21.8.2/114

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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BOTSWANA: S2

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