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1.3.1.1 Approved Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MEDROXYPROGESTERONE AURO 150 mg (injectable suspension).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Medroxyprogesterone Acetate USP 150 mg.

Sugar free.

Excipients with known effect:

Preservatives:

Methylparaben 0,14 % *m/v*

Propylparaben 0,015 % *m/v*

3. PHARMACEUTICAL FORM

MEDROXYPROGESTERONE AURO

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 **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** 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 MEDROXYPROGESTERONE AURO.

Switching from other methods of contraception

When switching from other contraceptive methods, **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** within 7 days after taking their last active pill).

Endometrial and renal carcinoma

Doses of 400 mg to 1000 mg of **MEDROXYPROGESTERONE AURO** 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 MEDROXYPROGESTERONE AURO. However, **MEDROXYPROGESTERONE AURO** 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 MEDROXYPROGESTERONE AURO. However, since **MEDROXYPROGESTERONE AURO** is almost exclusively eliminated by hepatic metabolism, no dosage adjustment should be necessary in women with renal insufficiency.

Paediatric population

MEDROXYPROGESTERONE AURO 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 **MEDROXYPROGESTERONE AURO** are expected to be the same for post-menarcheal adolescent and adult females.

Method of administration

MEDROXYPROGESTERONE AURO is administered intramuscularly.

The sterile aqueous suspension of **MEDROXYPROGESTERONE AURO** should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension of MEDROXYPROGESTERONE AURO.

4.3 Contraindications

- Known sensitivity to medroxyprogesterone acetate or any of the other ingredients of **MEDROXYPROGESTERONE AURO** (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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** 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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 medicine. 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 **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** in women with osteoporotic risk factors.
MEDROXYPROGESTERONE AURO 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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 medroxyprogesterone acetate as in MEDROXYPROGESTERONE AURO, 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 **MEDROXYPROGESTERONE AURO** 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 MEDROXYPROGESTERONE AURO. Decreases in serum estrogen due to **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** 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, **MEDROXYPROGESTERONE AURO** 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 medroxyprogesterone acetate as in MEDROXYPROGESTERONE AURO.

Bleeding irregularities

Most women receiving medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** for contraception experience disruption of menstrual bleeding patterns. It is recommended that medical practitioners or others directly responsible for patients using **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** continues, without other therapy being required.

Restoration of normal menstrual cycling may take from 5 to 28 months after the last injection of MEDROXYPROGESTERONE AURO.

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

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 **MEDROXYPROGESTERONE AURO** 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, **MEDROXYPROGESTERONE AURO** is not recommended for treatment of secondary amenorrhoea or dysfunctional uterine bleeding.

Central nervous system disorders
Mood changes and depression are side effects reported with the use of hormonal contraceptives including **MEDROXYPROGESTERONE AURO** (see section 4.8). There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behaviour (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with MEDROXYPROGESTERONE AURO.

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

Some patients may complain of premenstrual-like depression while on **MEDROXYPROGESTERONE AURO** therapy.

Carbohydrate metabolism

A decrease in glucose tolerance has been observed in patients on progestogens including medroxyprogesterone acetate as in MEDROXYPROGESTERONE AURO. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving **MEDROXYPROGESTERONE AURO** therapy.

Liver function

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

Weight changes

Weight gain may be associated with use of MEDROXYPROGESTERONE AURO.

Effects on laboratory tests

The pathologist should be advised of **MEDROXYPROGESTERONE AURO** therapy when relevant specimens are submitted.

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

- 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 **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** may exhibit suppressed adrenal function. **MEDROXYPROGESTERONE AURO** may decrease ACTH and hydrocortisone blood levels.

The high dose of **MEDROXYPROGESTERONE AURO** 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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** does not protect against sexually transmitted infections (STIs) including HIV infection (AIDS) or other sexually transmitted diseases but equally, **MEDROXYPROGESTERONE AURO** 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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** (150 mg IM every 12 weeks for 240 weeks) in adolescent females (12 – 18 years) for contraception showed that medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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.

Excipient information

Preservative sensitivity

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

***MEDROXYPROGESTERONE AURO** contains sodium*

MEDROXYPROGESTERONE AURO contains less than 1 mmol sodium (23 mg) per pre-filled syringe or vial, that is to say essentially 'sodium-free'

4.5 Interaction with other medicines and other forms of interaction

Aminoglutethimide administered concomitantly with **MEDROXYPROGESTERONE AURO** may significantly depress the bioavailability of MEDROXYPROGESTERONE AURO.

Medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 **MEDROXYPROGESTERONE AURO** have not been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy:

MEDROXYPROGESTERONE AURO is contraindicated in pregnancy (see section 4.3).

MEDROXYPROGESTERONE AURO should not be used as a diagnostic test for pregnancy.

Some reports suggest an association between intra-uterine exposure to progestational medicines, including medroxyprogesterone acetate as in MEDROXYPROGESTERONE AURO, 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 medroxyprogesterone acetate as in **MEDROXYPROGESTERONE AURO** 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 AURO** are uncommon.

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

Breastfeeding:

MEDROXYPROGESTERONE AURO 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 **MEDROXYPROGESTERONE AURO** on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

Tabulated list of adverse drug reactions

System Organ Class	Frequency	Undesirable effects
Immune system	Less frequent	Medicine hypersensitivity

disorders		Anaphylactic reaction, anaphylactoid reaction, angioedema
Endocrine disorders	Less frequent	Prolonged anovulation
Psychiatric disorders	Frequent	Nervousness
		Decreased libido, anorgasmia, depression, insomnia
Nervous system disorders	Frequent	Headache
		Dizziness
	Less frequent	Seizure, somnolence
Vascular disorders	Frequent	Hot flushes
	Less frequent	Thromboembolic disorders (thrombosis, embolism, thrombophlebitis and pulmonary embolism)
Gastrointestinal disorders	Frequent	Abdominal pain, abdominal discomfort
		Abdominal distension, nausea
	Less frequent	Diarrhoea
Hepato-biliary disorders	Less frequent	Jaundice, liver disorder
Skin and subcutaneous tissue disorders	Frequent	Rash, acne, alopecia
	Less frequent	Hirsutism, pruritis, urticaria

Musculoskeletal and connective tissue disorders	Frequent	Back pain, leg cramps
	Less frequent	Muscle cramps, arthralgia, muscle spasms
Reproductive system and breast disorders	Frequent	Dysfunctional uterine bleeding (irregular, increase, decrease, spotting), amenorrhoea
		Vaginal discharge, breast pain, breast tenderness, dysmenorrhoea, pelvic pain, vaginitis
	Less frequent	Galactorrhoea
		Cervix changes in erosion and secretion, virilisation, feminisation
General disorders and administration site conditions	Frequent	Fluid retention
		Asthenia, fatigue
	Less frequent	Pyrexia
		Injection-site reactions (pain, residual lumps and change in skin colour at site of injection)
Investigations	Frequent	Weight change
	Less frequent	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:		

Psychiatric disorders	Frequency unknown	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide
Skin and subcutaneous tissue disorders	Frequency unknown	Acquired lipodystrophy
Musculoskeletal and connective tissue disorders	Frequency unknown	Osteoporosis including osteoporotic fractures
General disorders and administration site conditions	Frequency unknown	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	Less frequent	Moon face
Metabolism and nutrition disorders	Frequent	Weight increase
Nervous system disorders	Frequent	Tremor
Vascular disorders	Less frequent	Thrombophlebitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis

Musculoskeletal and connective tissue disorders	Frequency unknown	Osteoporosis including osteoporotic fractures
Reproductive system and breast disorders	Less frequent	Dysfunctional vaginal bleeding (irregular, increased, decreased, spotting)
General disorders and administration site conditions	Frequent	Oedema/fluid retention
	Less frequent	Pyrexia
Investigations	Frequency unknown	Abnormal liver values
Oncology post-marketing reported side effects		
Psychiatric disorders	Frequency unknown	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide
Skin and subcutaneous tissue disorders	Frequency unknown	Acquired lipodystrophy
General disorders and administration site conditions	Frequency unknown	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. Healthcare providers are asked to

report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Medicine 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, headache have been attributed to therapeutic doses. Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacological classification: A 21.8.2 Progesterone with or without oestrogens

Pharmacotherapeutic group: Progestogens, ATC code: G03AC06

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.

5.3 Preclinical safety data

No data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The active substance is medroxyprogesterone acetate. The other ingredients of **MEDROXYPROGESTERONE AURO** are:

- Polyethylene Glycol 3350
- Polysorbate 80
- Sodium Chloride USP
- Methylparaben
- Propylparaben
- Sodium Hydroxide
- Hydrochloric Acid
- Water for injection
- Nitrogen

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

MEDROXYPROGESTERONE AURO:

White to off white suspension filled in 2.25 mL clear glass barrel with plastic rigid tip cap with luer lock and stoppered with black plunger stopper along with white plunger rod.

Medroxyprogesterone acetate injectable suspension, USP150 mg/mL [1mL Pre-filled syringe] is proposed to be marketed in 2.25 mL Glass Barrel with Plastic rigid tip cap with Luer Lok Adaptor, Plunger Rubber Stopper black chlorobutyl PH and Plunger ROD Plunger rod Ribbed-2.25 mL Barrel Medroxyprogesterone acetate injectable suspension, USP150 mg/mL [1mL Pre-filled syringe] shall be packed as per approved pack size. The PFS will be further packed in pre-printed carton with package leaflet.

Pack size: 1 vial.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd.

Woodhill Office Park, Building 1, First Floor,

53 Phillip Engelbrecht Avenue,

Meyersdal, Ext. 12, 1448,

Johannesburg,

South Africa.

8 REGISTRATION NUMBER(S)

56/21.8.2/1072

9 DATE OF FIRST AUTHORISATION

10 June 2025

10 DATE OF REVISION OF TEXT

Not applicable.