SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

DEPO-TESTOSTERONE™ 100 mg injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 100 mg testosterone cypionate.

Sugar free.

Each 10 mL vial of DEPO-TESTOSTERONE contains 94,5 mg (0,945 % m/v) benzyl alcohol as preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A pale yellow, oily solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DEPO-TESTOSTERONE is indicated for replacement therapy in adult males in conditions associated with deficiency or absence of endogenous testosterone.

1. Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.

2. Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumours, trauma, or radiation.

DEPO-TESTOSTERONE should not be used in children with delayed puberty or in adult men with age related hypogonadism as safety and efficacy have not been established (see section 4.4).

4.2 Posology and method of administration

Posology

Prior to initiating DEPO-TESTOSTERONE, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

Dosage will vary depending upon the age and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions.

For replacement in the hypogonadal male, 50 **-** 400 mg should be administered every two to four weeks.

Special populations

Elderly population

Elderly patients treated with DEPO-TESTOSTERONE may be at increased risk of developing prostatic hypertrophy and prostatic carcinoma (see section 4.4).

Paediatric population

Safety and effectiveness in children have not been established.

DEPO-TESTOSTERONE should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Warming and shaking the vial should re-dissolve any crystals that may have formed during storage at temperatures lower than recommended.

Method of administration

DEPO-TESTOSTERONE is for intramuscular use only. DEPO-TESTOSTERONE should not be given intravenously. Intramuscular injections should be given deep in the gluteal muscle.

4.3 Contraindications

- Hypersensitivity to testosterone cypionate or to any of the excipients in DEPO-TESTOSTERONE (listed in section 6.1)
- Males with carcinoma of the breast
- Males with known or suspected carcinoma of the prostate gland
- Patients with serious cardiac, hepatic or renal disease
- Hypercalcaemia
- Liver function impairment
- Pre-pubertal males
- Pregnancy and lactation (see section 4.6)
- Females of child-bearing potential

4.4 Special warnings and precautions for use

Hypercalcaemia may occur, especially in immobilised patients.

Prolonged use of high doses of DEPO-TESTOSTERONE has been associated with development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis - all potentially life-threatening complications.

Elderly patients treated with DEPO-TESTOSTERONE may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma.

There have been post-marketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients using DEPO-TESTOSTERONE. Evaluate patients who

report symptoms of pain, oedema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with DEPO-TESTOSTERONE and initiate appropriate workup and management.

Epidemiologic studies and randomised controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of DEPO-TESTOSTERONE compared to non-use. There is some evidence of an increased risk of MACE in association with use of testosterone replacement therapy in men especially with the use of testosterone as contained in DEPO-TESTOSTERONE for unapproved indications and/or with unapproved dosages (see section 4.8). Patients should be informed of this possible risk when deciding whether to use or to continue to use DEPO-TESTOSTERONE.

Abuse of DEPO-TESTOSTERONE and monitoring of serum testosterone concentrations

DEPO-TESTOSTERONE has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic, androgenic steroids. Anabolic, androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions (see section 4.8, Medicine abuse and dependence).

If DEPO-TESTOSTERONE abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of DEPO-TESTOSTERONE and anabolic, androgenic steroids. Conversely, consider the possibility of DEPO-TESTOSTERONE and anabolic, androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

DEPO-TESTOSTERONE should not be used concomitantly with anabolic, androgenic steroids.

Oedema, with or without congestive heart failure, may occur especially in patients with pre-existing cardiac, renal or hepatic disease (see section 4.3).

Due to the prolonged action of DEPO-TESTOSTERONE, it should be administered with caution to patients with organic heart disease of debilitation (see section 4.3).

Gynaecomastia may develop in patients being treated with DEPO-TESTOSTERONE for hypogonadism.

DEPO-TESTOSTERONE treatment can cause chorioretinopathy. Chorioretinopathy can lead to visual disturbances.

Androgen therapy should not be used in healthy males with delayed puberty. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature.

DEPO-TESTOSTERONE should not be used for the enhancement of athletic performance, because of the potential risk of serious adverse health effects.

General

Patients with benign prostatic hypertrophy given DEPO-TESTOSTERONE may develop acute urethral obstruction.

Priapism or excessive sexual stimulation may develop. Oligospermia and reduced ejaculatory volume may occur after prolonged administration or excessive dosage. Hypersensitivity and gynaecomastia may occur. If any of these effects appear, DEPO-TESTOSTERONE should be stopped.

DEPO-TESTOSTERONE should not be used interchangeably with testosterone propionate, enanthate or phenylacetate because of differences in duration of action.

DEPO-TESTOSTERONE is not for intravenous use.

Patients should be instructed to report any of the following: nausea, vomiting, changes in skin colour, ankle swelling, too frequent or persistent erections of the penis.

Laboratory tests

Haemoglobin and haematocrit levels (to detect polycythaemia) should be checked periodically in patients receiving long-term DEPO-TESTOSTERONE administration.

Serum cholesterol may increase during DEPO-TESTOSTERONE therapy.

Dependence

Behaviours associated with addiction:

Continued abuse of DEPO-TESTOSTERONE and other anabolic, androgenic steroids, leading to addiction is characterised by the following behaviours:

- Taking greater dosages than prescribed
- Continued medicine use despite medical and social problems due to medicine use
- Spending significant time to obtain the medicine when supplies of the medicine are interrupted
- Giving a higher priority to medicine use than other obligations
- Having difficulty in discontinuing the medicine despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterised by withdrawal symptoms after abrupt medicine discontinuation or a significant dose reduction of a medicine. Individuals taking supratherapeutic doses of DEPO-TESTOSTERONE may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Medicine dependence in individuals using approved doses of DEPO-TESTOSTERONE for approved indications has not been documented.

Excipients

The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in paediatric patients. Although normal therapeutic doses of this medicine ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

4.5 Interaction with other medicines and other forms of interaction

DEPO-TESTOSTERONE may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinaemia.

In diabetic patients, the metabolic effects of DEPO-TESTOSTERONE may decrease blood glucose and, therefore, insulin requirements.

Medicine/laboratory test interferences

DEPO-TESTOSTERONE may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

4.6 Fertility, pregnancy and lactation

DEPO-TESTOSTERONE is contraindicated in pregnancy and lactation (see section 4.3).

Benzyl alcohol can cross the placenta (see section 4.4).

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following adverse reactions in males may occur:

System organ class	Adverse event
Blood and the lymphatic system disorders	Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, polycythaemia
Immune system disorders	Hypersensitivity, including skin manifestations and anaphylactoid reactions
Metabolism and nutrition disorders	Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates, hypercalcaemia
Psychiatric disorders	Increased or decreased libido, headache, anxiety, depression
Nervous system disorders	Paraesthesia
Eye disorders	Chorioretinopathy (see section 4.4)
Cardiac disorders	Myocardial infarction, stroke
Vascular disorders	Deep vein thrombosis, pulmonary embolism
Gastrointestinal disorders	Nausea
Hepato-biliary disorders	Cholestatic jaundice, alterations in liver function tests, hepatocellular benign and malignant neoplasms, peliosis hepatis (see section 4.4)
Skin and subcutaneous tissue disorders	Hirsutism, male pattern of baldness, seborrhoea, acne

Reproductive system and breast disorders	Gynaecomastia, excessive frequency and duration of penile erections, priapism, decreased ejaculatory volume. Oligospermia may occur at high dosages
General disorders and administration site conditions	Oedema, inflammation and pain at the site of intramuscular injection

The Penile Brachial Index (PBI) may increase during DEPO-TESTOSTERONE therapy without clinical significance.

Medicine abuse and dependence

Abuse

Abuse and misuse of DEPO-TESTOSTERONE may occur often in combination with other anabolic androgenic steroids (AAS).

Abuse-related adverse reactions

Serious adverse reactions have been reported in individuals who abuse anabolic, androgenic steroids and include:

System organ class	**Adverse event**
Psychiatric disorders	Serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression
Nervous system disorders	Cerebrovascular accident
Cardiac disorders	Cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure
Hepato-biliary disorders	Hepatotoxicity

The following adverse reactions have also been reported in men

System organ class	**Adverse event**
Psychiatric disorders	Hypomania, irritability
Nervous system disorders	Transient ischaemic attacks, convulsions
Reproductive system and breast disorders	Testicular atrophy, subfertility, infertility
Investigations	Dyslipidaemias

The following additional adverse reactions have been reported in women

System organ class	**Adverse event**
Endocrine disorders	Virilisation
Respiratory, thoracic and mediastinal disorders	Deepening of voice
Skin and subcutaneous tissue disorders	Hirsutism, male-pattern baldness
Reproductive system and breast disorders	Clitoral enlargement, breast atrophy, menstrual irregularities

The following adverse reactions have been reported in male and female adolescents

System organ class	**Adverse event**
Endocrine disorders	Precocious puberty
Musculoskeletal, connective tissue and bone disorders	Premature closure of bony epiphyses with termination of growth

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other medicines, it is not always possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

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

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.7 Male sex hormones

Mechanism of action

Testosterone is an androgen. During exogenous administration of testosterone cypionate, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinising hormone (LH). At large doses of testosterone cypionate, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

5.2 Pharmacokinetic properties

Absorption

Testosterone cypionate injected intramuscularly is absorbed slowly from the lipid phase.

Distribution

Testosterone in plasma is 98 % bound to a specific testosterone-oestradiol binding globulin, and about 2 % is free. The amount of this sex-hormone binding globulin in the plasma influences the distribution of testosterone between free and bound forms and the free testosterone concentration will determine its half-life.

Elimination

About 90 % of a dose of testosterone is excreted in the urine as glucuronic and sulphuric acid conjugates of testosterone and its metabolites; about 6 % of a dose is excreted in the faeces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolised to various 17-keto steroids through two different pathways.

The half-life of testosterone cypionate when injected intramuscularly is approximately 8 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Benzyl benzoate

Cottonseed oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

6.5 Nature and contents of the pack

DEPO-TESTOSTERONE 100 mg is available in a 10 mL vial sealed with a grey rubber stopper and secured with an aluminium overseal with a flip-off cap. Each vial is packed in an outer cardboard carton.

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. REFERENCE NUMBER

G2989 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

N/A – Old medicine

10. DATE OF REVISION OF THE TEXT

11 February 2021

Manufacturer: Pharmacia and Upjohn Company LLC, Kalamazoo, USA