PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TESTOSTERONE PD Oily solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule/vial contains testosterone undecanoate 1000 mg in a 4 mL solution for injection (testosterone undecanoate 250 mg/mL, corresponding to 157.9 mg of testosterone base form).

TESTOSTERONE PD is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, yellowish oily solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Testosterone replacement in primary and secondary male hypogonadism.

4.2 Posology and method of administration

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TESTOSTERONE PD (1 ampoule/vial corresponding to testosterone undecanoate 1000 mg) is injected every 10 to 14 weeks. Injections with this frequency are capable of maintaining sufficient testosterone levels and do not lead to accumulation.

Start of treatment

Serum testosterone levels should be measured before the start of treatment. The first injection interval may be reduced to a minimum of 6 weeks depending on serum testosterone levels and clinical symptoms. With this loading dose, steady-state levels will be reached quickly.

Individualisation of treatment

It is advisable to occasionally measure testosterone serum levels at the end of an injection interval.

Serum levels below normal range would indicate the need for a shorter injection interval. In the case of high serum levels, an extension of the injection interval may be considered. The injection interval should remain within the recommended range of 10 to 14 weeks.

Special populations

Elderly

Limited data do not suggest the need for a dosage adjustment in elderly patients (see section 4.4).

Hepatic impairment

No formal studies have been performed in patients with hepatic impairment. The use of TESTOSTERONE PD is contraindicated in men with past or present liver tumours (see section 4.3).

Renal impairment

No formal studies have been performed in patients with renal impairment.

Paediatric population

TESTOSTERONE PD is not indicated for use in children and adolescents and it has not been clinically evaluated in males under 18 years of age (see section 4.4).

Method of administration

For intramuscular use.

The injections must be administered very slowly (over two minutes). TESTOSTERONE PD is strictly for intramuscular injection. Special care must be given to avoid intravasal injection. See section 6.6 to avoid injury when opening. The content of an ampoule/vial are to be injected intramuscularly immediately after opening.

4.3 Contraindications

- hypersensitivity to testosterone undecanoate or to any of the ingredients of TESTOSTERONE PD (see section 6.1)
- androgen-dependent carcinoma of the prostate or of the male mammary gland
- past or present liver tumours
- hypercalcaemia accompanying malignant tumours.

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The use of TESTOSTERONE PD in women is contraindicated.

4.4 Special warnings and precautions for use

There may be an increased risk for the development of prostatic hyperplasia in older patients treated with TESTOSTERONE PD. Although there are no clear indications that TESTOSTERONE PD actually, generates prostatic carcinoma, it can enhance the growth of any existing prostatic carcinoma. Therefore before starting therapy with TESTOSTERONE PD, carcinoma of the prostate has to be excluded.

TESTOSTERONE PD should be used only if hypogonadism (hyper- and hypogonadotropic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction etc.) and confirmed by two separate blood testosterone measurements.

Medical examinations

Prior to TESTOSTERONE PD initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breasts must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).

Laboratory tests

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Testosterone level should be monitored at baseline and at regular intervals during TESTOSTERONE PD treatment. Healthcare practitioners should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin and haematocrit (to detect cases of polycythaemia), liver function tests and lipid profile (see section 4.8).

Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Tumours

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

TESTOSTERONE PD should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.

Benign liver tumours and malignant liver tumours have been reported in users of hormonal substances, for example, testosterone compounds. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in men using TESTOSTERONE PD.

Cardiac, hepatic or renal insufficiency

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment with TESTOSTERONE PD must be stopped immediately.

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Hepatic or renal insufficiency

There are no studies undertaken to demonstrate the efficacy and safety of TESTOSTERONE PD in patients with renal or hepatic impairment. Therefore, testosterone replacement therapy should be used with caution in these patients.

Cardiac insufficiency

Caution should be exercised in patients predisposed to oedema, e.g. in case of severe cardiac, hepatic, or renal insufficiency or ischemic heart disease, as treatment with TESTOSTERONE PD may result in increased retention of sodium and water. In case of severe complications characterized by oedema with or without congestive heart failure treatment must be stopped immediately (see section 4.8).

Testosterone may cause a rise in blood pressure and TESTOSTERONE PD should be used with caution in men with hypertension.

Clotting disorders

As a general rule, the limitations of using intramuscular injections in patients with acquired or inherited bleeding disorders always have to be observed.

Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants (see also section 4.5)

Testosterone, as in TESTOSTERONE PD, should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and reports of thrombotic events (e.g. deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore

continuing TESTOSTERONE PD treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimise the individual VTE risk.

Other conditions

TESTOSTERONE PD should be used with caution in patients with epilepsy and migraine, as the conditions may be aggravated.

Improved insulin sensitivity may occur in patients treated with TESTOSTERONE PD who achieve normal testosterone plasma concentrations following replacement therapy.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive TESTOSTERONE PD exposure, requiring dosage adjustment.

Pre-existing sleep apnoea may be potentiated.

Athletes treated for testosterone replacement in primary and secondary male hypogonadism should be advised that TESTOSTERONE PD contains an active substance which may produce a positive reaction in anti-doping tests.

TESTOSTERONE PD is not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

TESTOSTERONE PD should be permanently withdrawn if symptoms of excessive androgen exposure persist or reappear during treatment with the recommended dosage regimen.

PROFESSIONAL INFORMATION

Suspected anaphylactic reactions after TESTOSTERONE PD injection have been reported.

Pulmonary micro embolism of oily solutions can in cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible.

Drug abuse and dependence

Testosterone, as contained in TESTOSTERONE PD, has been subject to abuse, typically at doses higher than recommended for the approved indication(s) and in combination with other anabolic androgenic steroids.

Abuse of testosterone and other anabolic androgenic steroids can lead to serious adverse reactions including: cardiovascular (with fatal outcomes in some cases), hepatic and/or psychiatric events.

Testosterone abuse may result in dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use. The abuse of testosterone and other anabolic androgenic steroids carries serious health risks and is to be discouraged.

Paediatric population

Clinical trials with TESTOSTERONE PD in children or adolescents under the age of 18 have not been conducted so far.

In children, besides masculinisation, TESTOSTERONE PD can cause accelerated growth and bone maturation and premature epiphyseal closure, thereby reducing final height.

PROFESSIONAL INFORMATION

4.5 Interaction with other medicines and other forms of interaction

Hypoglycaemics

TESTOSTERONE PD may enhance the blood-sugar reducing effects of insulin. The dosage of the hypoglycaemic medicine may need to be lowered.

Barbiturates and other enzyme inducers

Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of TESTOSTERONE PD (e.g. barbiturates).

Oral anticoagulants

Testosterone and derivatives, such as TESTOSTERONE PD have been reported to increase the activity of coumarin derived oral anticoagulants, possibly requiring dose adjustment. Independently of this finding, as a general rule, the limitations of using intramuscular injections in patients with acquired or inherited blood clotting irregularities always have to be observed, especially at the beginning or end of TESTOSTERONE PD therapy. Increased monitoring of the prothrombin time, and INR determinations, are recommended.

Oxyphenbutazone

Increased oxyphenbutazone serum levels have been reported.

Other interactions

The concurrent administration of TESTOSTERONE PD with ACTH or corticosteroids may enhance oedema formation; thus these medicines should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema.

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Laboratory test interactions:

TESTOSTERONE PD may decrease levels of thyroxin-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

Not applicable. TESTOSTERONE PD is not indicated for use in women.

Fertility

Testosterone replacement therapy as in TESTOSTERONE PD may reversibly reduce spermatogenesis (see section 4.8).

4.7 Effects on ability to drive and use machines

Dizziness has been reported as an uncommon side effect (see section 4.8). Patients experiencing dizziness should avoid driving and use of machine.

4.8 Undesirable effects

a). Summary of the safety profile

The most frequently reported undesirable effects during treatment with TESTOSTERONE PD are acne and injection site pain.

Pulmonary micro embolism can occur after TESTOSTERONE PD injection (see section 4.4). Suspected anaphylactic reactions after TESTOSTERONE PD injection have been reported.

PROFESSIONAL INFORMATION

TESTOSTERONE PD may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

b). Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequent Less frequent	Polycythaemia Haematocrit increased*, red blood cell count increased*, haemoglobin increased*
Immune system disorders	Less frequent	Hypersensitivity
Metabolism and nutrition disorders	Frequent Less frequent	Weight gain Increased appetite, glycosylated haemoglobin increased, hypercholesterolaemia, blood triglycerides increased
Psychiatric disorders	Less frequent Frequency unknown	Depression, emotional disorder, insomnia, restlessness, aggression, irritability Nervousness, hostility
Nervous system disorders	Less frequent	Headache, migraine, tremor
Vascular disorders	Frequent Less frequent	Hot flush Cardiovascular disorder, hypertension, dizziness
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent Frequency unknown	Respiratory disorder Bronchitis, sinusitis, cough, dyspnoea, snoring, dysphonia Sleep apnoea

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Gastrointestinal disorders	Less frequent	Nausea, diarrhoea
Hepatobiliary disorders	Less frequent	Jaundice, liver function test abnormalities, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Acne, Alopecia, erythema, rash, dry skin, pruritus, papular rash Seborrhoea
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Arthralgia, pain in extremity, muscle disorders (including muscle spasm, muscle strain and myalgia), musculoskeletal stiffness, blood creatine phosphokinase increased Muscle cramps
Renal and urinary disorders	Less frequent	Urine flow decreased, urinary retention, urinary tract disorder, nocturia, dysuria
Reproductive system and breast disorders	Frequent Less frequent Frequency unknown	Prostate specific antigen increased, prostate examination abnormal, benign prostate hyperplasia Prostatic intraepithelial neoplasia, prostate induration, prostatitis, prostatic disorder, testicular pain, breast induration, breast pain, gynaecomastia, estradiol increased, testosterone increased, increased libido, decreased libido Increased frequency of erections, reversible interrupted or reduced spermatogenesis, thereby reducing the size of the testicles, persistent painful erections (priapism)

PROFESSIONAL INFORMATION

General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Injection site pain, subcutaneous haematoma at the injection site Fatigue, asthenia, hyperhidrosis, night sweats Water retention, oedema
Injury and poisoning	Less frequent	Pulmonary oil micro-embolism

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 Med Safety APP (Medsafety X SAHPRA) and e Reporting platform (who-umc.org) found on the SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

No special therapeutic measure apart from termination of therapy with TESTOSTERONE PD or dose reduction is necessary after overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, 3-oxoandrosten (4) derivatives

ATC code: G03BA03

PROFESSIONAL INFORMATION

Pharmacological classification: A. 21.7 Male sex hormones.

Mechanism of action

Testosterone undecanoate is an ester of the naturally occurring androgen, testosterone. The active form testosterone, is formed by cleavage of the side chain.

Testosterone is the most important androgen of the male, mainly synthesized in the testicles, and to a small extent in the adrenal cortex.

Testosterone is responsible for the expression of masculine characteristics during foetal, early childhood, and pubertal development and thereafter for maintaining the masculine phenotype and androgen-dependent functions (e.g. spermatogenesis, accessory sexual glands). It also performs functions, e.g. in the skin, muscles, skeleton, kidney, liver, bone marrow, and CNS.

Dependent on the target organ, the spectrum of activities of testosterone is mainly androgenic (e.g. prostate, seminal vesicles, epididymis) or protein-anabolic (muscle, bone, haematopoiesis, kidney, liver).

The effects of testosterone in some organs arise after peripheral conversion of testosterone to estradiol, which then binds to estrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone, and testicular Leydig cells.

5.2 Pharmacokinetic properties

Absorption:

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This is an intramuscularly administered depot preparation of testosterone undecanoate and thus circumvents the first-pass effect. Following intramuscular injection of testosterone undecanoate as an oily solution, the compound is gradually released from the depot and is almost completely cleaved by serum esterases into testosterone and undecanoic acid. An increase of serum levels of testosterone above basal values can already be measured one day after administration.

Distribution:

In two separate studies, mean maximum concentrations of testosterone of 24 and 45 nmol/L were measured about 14 and 7 days, respectively, after single i.m. administration of 1000 mg of testosterone undecanoate to hypogonadal men. Post maximum testosterone levels declined with an estimated half-life of about 53 days.

In the serum of men, about 98 % of the circulating testosterone is bound to SHBG and albumin. Only the free fraction of testosterone is considered as biologically active. Following intravenous infusion of testosterone to elderly men, an apparent volume of distribution of about 1,0 L/kg was determined.

Biotransformation:

Testosterone which is generated by ester cleavage from testosterone undecanoate is metabolised and excreted the same way as endogenous testosterone. The undecanoic acid is metabolised by β-oxidation in the same way as other aliphatic carboxylic acids.
The major active metabolites of testosterone are estradiol and dihydrotestosterone.

Elimination:

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Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the administration of radio-labelled testosterone, about 90 % of the radioactivity appears in the urine as glucuronic and sulphuric acid conjugates and 6 % appears in the faeces after undergoing enterohepatic circulation. Urinary products include androsterone and etiocholanolone.

Steady-state conditions

Following repeated intramuscular injection of 1000 mg testosterone undecanoate to hypogonadal men using an interval of 10 weeks between two injections, steady-state conditions were achieved between the 3rd and the 5th administration. Mean C_{max} and C_{min} values of testosterone at steady-state were about 42 and 17 nmol/L, respectively. Post-maximum testosterone levels in the serum decreased with a half-life of about 90 days, which corresponds to the release rate from the depot.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl benzoate

Castor oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

PROFESSIONAL INFORMATION

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

Amber glass vial with a dark grey coated coated elastomer injection stopper sealed with a grey aluminium flip-off cap with white plastic button without engraving.

Pack size: 1 x 4 mL.

6.6 Special precautions for disposal

At cold storage temperatures the properties of this oil-based solution might temporarily change (e.g. higher viscosity, cloudiness). If stored at cold temperature, TESTOSTERONE PD should be brought to room or body temperature before use.

The solution for intramuscular injection is to be visually inspected prior to use and only clear solutions free from particles should be used.

TESTOSTERONE PD is for single use only and any unused solution should be discarded in accordance with local requirements.

The vial is for single use only. The content of a vial is to be injected intramuscularly immediately after drawing up into the syringe. After removal of the plastic cap (A) do not remove the metal ring (B) or the crimp cap (C).

PROFESSIONAL INFORMATION

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

57/21.7/0452

9. DATE OF FIRST AUTHORISATION

24 June 2024