SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Testosterone Teva 1000 mg/4 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for injection contains 250 mg testosterone undecanoate corresponding to 157.9 mg testosterone.

Each vial with 4 ml solution for injection contains 1000 mg testosterone undecanoate corresponding to 631.5 mg testosterone.

Excipient with known effect:
2000 mg benzyl benzoate per vial.

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 therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests (see section 4.4).

4.2 Posology and method of administration

Posology

One vial of <Product name> (corresponding to 1000 mg testosterone undecanoate) 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 start and during initiation of treatment. Depending on serum testosterone levels and clinical symptoms, the first injection interval may be reduced to a minimum of 6 weeks as compared to the recommended range of 10 to 14 weeks for maintenance. With this loading dose, sufficient steady state testosterone levels may be achieved more rapidly.

Maintenance and individualisation of treatment
The injection interval should be within the recommended range of 10 to 14 weeks. Careful monitoring of serum testosterone levels is required during maintenance of treatment. It is advisable to measure testosterone serum levels regularly. Measurements should be performed at the end of an injection interval and clinical symptoms considered. These serum levels should be within the lower third of the normal range. Serum levels below normal range would indicate the need for a shorter injection interval. In case of high serum levels an extension of the injection interval may be considered.

Special populations

Paediatric population
<Product name> 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).

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

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

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

Method of administration

For intramuscular use.

The injections must be administered very slowly (over two minutes). <Product name> is strictly for intramuscular injection. Care should be taken to inject <Product name> deeply into the gluteal muscle following the usual precautions for intramuscular administration. Special care must be taken to avoid intravasal injection (see section 4.4 under "Application"). The contents of a vial are to be injected intramuscularly immediately after opening.

4.3 Contraindications

The use of <Product name> is contraindicated in men with:

- androgen-dependent carcinoma of the prostate or of the male mammary gland
- past or present liver tumours
- hypersensitivity to the active substance or to any of the excipients (listed in section 6.1).

The use of <Product name> in women is contraindicated.

4.4 Special warnings and precautions for use

<Product name> is not recommended for use in children and adolescents.

<Product name> should be used only if hypogonadism (hyper- and hypogonadotrophic) 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.

Elderly population
There is limited experience on the safety and efficacy of the use of <Product name> in patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

Medical examination and laboratory tests

Medical examinations

Prior to testosterone 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 breast 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). Local guidelines for safety monitoring under testosterone replacement therapy should be taken into consideration.

Laboratory tests
Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians 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, 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.

<Product name> 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.

Cases of benign and malignant liver tumours have been reported in users of hormonal substances such as androgen compounds. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur in men using <Product name>, a liver tumour should be included in the differential-diagnostic considerations.

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

Hepatic or renal insufficiency
There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product 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 ischaemic heart disease, as treatment with androgens 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 <Product name> 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 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 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
<Product name> 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 androgens who achieve normal testosterone plasma concentrations following replacement therapy. Therefore, the dosage of hypoglycaemic agents may need to be lowered.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen 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 the medicinal product contains an active substance which may produce a positive reaction in anti-doping tests.

Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

<Product name> should be permanently withdrawn if symptoms of excessive androgen exposure persist or reappear during treatment with the recommended dosage regimen.

Drug abuse and dependence
Testosterone 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.

Application
As with all oily solutions, <Product name> must be injected strictly intramuscularly and very slowly (over two minutes). Pulmonary microembolism of oily solutions can in rare 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. The patient should therefore be observed during and immediately after each injection in order to allow for early recognition of possible signs and symptoms of pulmonary oily microembolism. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

Suspected anaphylactic reactions after <Product name> injection have been reported.

Information about excipients
This medicine contains 2000 mg Benzyl benzoate in each 4 ml vial which is equivalent to 500 mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anti-coagulants
Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anti-coagulants. Patients receiving oral anti-coagulants require close monitoring, especially at the beginning or end of androgen therapy. Increased monitoring of the prothrombin time, and INR determinations, are recommended.

Other interactions
The concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation; thus these active substances should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema.

Laboratory test interactions: Androgens 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

Fertility
Testosterone replacement therapy may reversibly reduce spermatogenesis (see sections 4.8 and 5.3).

Pregnancy and breastfeeding
<Product name> is not indicated for use in women and must not be used in pregnant or breast-feeding women (see section 4.3).

4.7 Effects on ability to drive and use machines

<Product name> has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Regarding undesirable effects associated with the use of androgens, please also refer to section 4.4.

The most frequently reported undesirable effects during treatment with <Product name> are acne and injection site pain.

Pulmonary microembolism of oily solutions can in rare 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. Cases suspected by the company or the reporter to represent oily pulmonary microembolism have been reported rarely in clinical trials (in ≥ 1/10,000 and < 1/1,000 injections) as well as from postmarketing experience (see section 4.4).

Suspected anaphylactic reactions after <Product name> injection have been reported.

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

Table 1 below reports adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs) reported with <Product name>. The frequencies are based on clinical trial data and defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs were recorded in 6 clinical studies (N=422) and considered at least possibly causally related to <Product name>.

Tabulated list of adverse reactions

Table 1: Categorised relative frequency of men with ADRs, by MedDRA SOC – based on pooled data of six, clinical trials, N=422 (100.0%), i.e. N=302 hypogonadal men treated with i.m. injections of 4 ml and N=120 with 3 ml of TU 250 mg/ml

System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Blood and lymphatic system disorders	Polycythaemia Haematocrit increased* Red blood cell count increased* Haemoglobin increased*		
Immune system disorders		Hypersensitivity	
Metabolism and nutrition disorders	Weight increased	Increased appetite Glycosylated haemoglobin increased Hypercholesterolaemia Blood triglycerides increased Blood cholesterol increased	
Psychiatric disorders		Depression Emotional disorder Insomnia Restlessness Aggression Irritability	
Nervous system disorders		Headache Migraine Tremor	
Vascular disorders	Hot flush	Cardiovascular disorder Hypertension Dizziness	
Respiratory, thoracic and mediastinal disorders		Bronchitis Sinusitis Cough Dyspnoea Snoring Dysphonia	
Gastrointestinal disorders		Diarrhoea Nausea	
Hepatobiliary disorders		Liver function test abnormal Aspartate aminotransferase increased	
Skin and subcutaneous tissue disorders	Acne	Alopecia Erythema Rash[1] Pruritus Dry skin	
Musculoskeletal and connective tissue disorders		Arthralgia Pain in extremity Muscle disorder[2] Musculoskeletal stiffness Blood creatine phosphokinase increased	
Renal and urinary		Urine flow decreased	

disorders		Urinary retention Urinary tract disorder Nocturia Dysuria	
Reproductive system and breast disorders	Prostatic specific antigen increased Prostate examination abnormal Benign prostatic hyperplasia	Prostatic dysplasia Prostate induration Prostatitis Prostatic disorder Libido disorder Testicular pain Breast induration Breast pain Gynaecomastia Oestradiol increased Blood testosterone increased	
General disorders and administration site conditions	Various kinds of injection site reactions[3]	Fatigue Asthenia Hyperhidrosis[4]	
Injury, poisoning and procedural complications			Pulmonary oil microembolism**

*Respective frequency has been observed in relation to the use in testosterone containing products.
**Frequency is based on the number of injections.

The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

[1] Rash including Rash papular
[2] Muscle disorder: Muscle spasms, Muscle strain and Myalgia
[3] Various kinds of injection site reaction: Injection site pain, Injection site discomfort, Injection site pruritus, Injection site erythema, Injection site haematoma, Injection site irritation, Injection site reaction
[4] Hyperhidrosis: Hyperhidrosis and Night sweats

Description of selected adverse reactions
Pulmonary microembolism of oily solutions can in rare 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 injections and are reversible. Cases suspected by the company or the reporter to represent oily pulmonary microembolism have been reported rarely in clinical trials (in ≥ 1/10,000 and < 1/1,000 injections) as well as from post-marketing experience (see section 4.4).

In addition to the above mentioned adverse reactions, nervousness, hostility, sleep apnoea, various skin reactions including seborrhoea, increased hair growth, increased frequency of erections and in very rare cases jaundice have been reported under treatment with testosterone containing preparations.

Therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism). High-dosed or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No special therapeutic measure apart from termination of therapy with the medicinal product or dose reduction is necessary after overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, 3-oxoandrosten (4) derivatives
ATC code: G03B A03

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 synthesised 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 oestradiol, 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
<Product name> 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 in serum levels of testosterone above basal values may be seen one day after administration.

Steady-state conditions
After the 1st intramuscular injection of 1000 mg testosterone undecanoate to hypogonadal men, mean C_{max} values of 38 nmol/L (11 ng/ml) were obtained after 7 days. The second dose was administered 6 weeks after the 1st injection and maximum testosterone concentrations of about 50 nmol/l (15 ng/ml) were reached. A constant dosing interval of 10 weeks was maintained during the following 3 administrations and 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 37 (11 ng/ml) and 16 nmol/l (5 ng/ml), respectively. The median intra- and inter-individual variability (coefficient of variation, %) of C_{min} values was 22% (range: 9-28%) and 34% (range: 25-48%), respectively.

Distribution
In serum of men, about 98% of the circulating testosterone is bound to sex hormone binding globulin (SHBG) and albumin. Only the free fraction of testosterone is considered as biologically active.

Following intravenous infusion of testosterone to elderly men, the elimination half-life of testosterone was approximately one hour and 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 ß-oxidation in the same way as other aliphatic carboxylic acids. The major active metabolites of testosterone are oestradiol and dihydrotestosterone.

Elimination
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 medicinal products include androsterone and etiocholanolone. Following intramuscular administration of this depot formulation the release rate is characterised by a half life of 90±40 days.

5.3 Preclinical safety data

Toxicological studies have not revealed other effects than those which can be explained based on the hormone profile of <Product name>.

Testosterone has been found to be non-mutagenic in vitro using the reverse mutation model (Ames test) or hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in studies on laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone.

Sex hormones are known to facilitate the development of certain tumours induced by known carcinogenic agents. The clinical relevance of the latter observation is not known.

Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose dependent manner.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl benzoate
Castor oil, refined

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years
The medicinal product must be used immediately after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass vial with a bromobutyl injection stopper sealed with an aluminium flip-off cap with orange plastic disk.

Pack size: 1 x 4 ml.

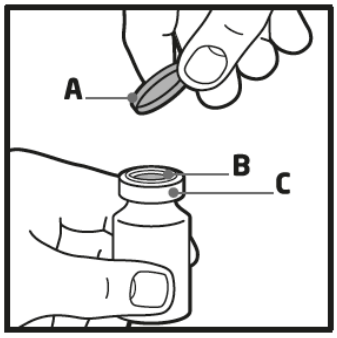
6.6 Special precautions for disposal and other handling

At cold storage temperatures the properties of this oil-based solution might temporarily change (e.g. higher viscosity, cloudiness). If stored at cold temperature, the product 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.

The medicinal product 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).



7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2023-07-18