T-HIM Depot Injection (Testosterone undecanoate)

Black Box Warning: Serious Pulmonary Oil Microembolism (Pome) Reactions And Anaphylaxis

Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.

Following each injection of T-HIM, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis.

Composition

T-HIM Depot Injection
Each ml contains:
Testosterone Undecanoate ....... 250 mg
(equivalent to Testosterone......157.9 mg)
Oily excipients ................................. q.s.

Dosage Form

Intramuscular Injection

Pharmacology

Mechanism of Action
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 (e.g. normal growth and development of male sex organs) during foetal, early childhood, and pubertal development and thereafter for maintaining the masculine phenotype (e.g. maintenance of secondary sex characteristics such as the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal development, vocal cord thickening, and alterations in body musculature and fat distribution) 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 central nervous system (CNS).
Dependent on the target organ, the spectrum of activities of testosterone is mainly androgenic (e.g. growth and
maturation of prostate, seminal vesicles, epididymis, penis, and scrotum) 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 oestrogen receptors in the target cell nucleus, e.g. the pituitary, fat, brain, bone, and testicular Leydig cells.

Absorption
T-HIM Depot Injection 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 tissue esterases into testosterone and undecanoic acid. An increase in serum levels of testosterone above basal values may be seen one day after administration.

After the first intramuscular injection of 1,000 mg testosterone undecanoate to hypogonadal men, mean $C_{\text{max}}$ values of 38 nmol/L (11 ng/mL) were obtained after 7 days. The second dose was administered 6 weeks after the first 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 three administrations and steady-state conditions were achieved between the third and the fifth administration. Mean $C_{\text{max}}$ and $C_{\text{min}}$ 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 $C_{\text{min}}$ values was 22 % (range: 9–28%) and 34% (range: 25–48%), respectively.

Distribution
In the 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 1 hour and an apparent volume of distribution of about 1.0 l/kg was determined.

Metabolism
Testosterone that is generated by ester cleavage from testosterone undecanoate is metabolized and excreted the same way as endogenous testosterone. The undecanoic acid is metabolised by $\beta$-oxidation in the same way as other aliphatic carboxylic acids. The major active metabolites of testosterone are oestradiol and dihydrotestosterone.

Excretion
Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the administration of radiolabelled 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 characterized by a half-life of 90±40 days.

Effect of Body Weight and Body Mass Index (BMI)
Analysis of serum testosterone concentrations from 117 hypogonadal men in the 84-week clinical study of testosterone undecanoate indicated that serum testosterone concentrations achieved were inversely correlated with the patient’s body weight. In 60 patients with pretreatment body weight of ≥100 kg, the mean (±SD) serum testosterone average concentration was 426 ± 104 ng/dL. A higher serum testosterone average concentration (568 ± 139 ng/dL) was observed in 57 patients weighing 65 to 100 kg. A similar trend was also observed for maximum serum testosterone concentrations.

In 70 patients with pretreatment body mass index of >30 kg/m², the mean (±SD) serum testosterone average concentration was 445 ± 116 ng/dL. Higher serum testosterone average concentrations (579 ± 101 ng/dL and 567± 155 ng/dL) were observed in patients with BMIs <26 kg/m² and 26 to 30 kg/m² respectively. A similar trend was also
observed for maximum serum testosterone concentrations.

Special Populations

Paediatric
T-HIM Depot Injection is not indicated for use in children and adolescents and it has not been clinically evaluated in males under 18 years of age.

Geriatric
Limited data do not suggest the need for a dosage adjustment in elderly patients.

Hepatic Impairment
No formal studies have been performed in patients with hepatic impairment. The use of testosterone undecanoate is contraindicated in men with past or present liver tumours.

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

Indications

T-HIM Depot Injection is indicated for testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features or biochemical tests.
T-HIM Depot Injection should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

Limitations of Use:

Safety and efficacy of testosterone undecanoate in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.
Safety and efficacy of testosterone undecanoate in males less than 18 years old have not been established.

Dosage And Administration

Prior to initiating testosterone replacement therapy with testosterone undecanoate injection, 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.
One vial of T-HIM Depot Injection (corresponding to 1,000 mg testosterone undecanoate) is injected intraglutteally every 10–14 weeks. Dosage titration is not necessary. Injections with this frequency are capable of maintaining sufficient testosterone levels and do not lead to accumulation.
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 with the recommended range of 10–14 weeks for maintenance. With this loading dose, sufficient steady-state testosterone levels may be achieved more rapidly.
The injection interval should be within the recommended range of 10–14 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.

Method of Administration
For intramuscular use only.
The injections must be administered very slowly (over 2 minutes). T-HIM Depot Injection is strictly for intramuscular injection. Care should be taken to inject T-HIM Depot Injection deeply into the gluteal muscle, following the usual precautions for intramuscular administration. Special care must be taken to avoid intravascular injection as this may lead to pulmonary microembolism. The contents of an ampoule/vial are to be injected intramuscularly immediately after opening. After having drawn up the testosterone undecanoate solution from the vial, expel excess air bubbles from the syringe. Replace the syringe needle used to draw up the solution from the vial with a new intramuscular needle and inject. Discard any unused portion in the vial.

T-HIM Depot Injection should be inspected visually for particulate matter and discoloration prior to administration and only clear solutions free from particles should be used.

The site for injection for testosterone undecanoate is the gluteus medius muscle site located in the upper outer quadrant of the buttock. Care must be taken to avoid the needle hitting the superior gluteal arteries and sciatic nerve. Between consecutive injections, alternate the injection site between left and right buttock.

Following antiseptic skin preparation, enter the muscle and maintain the syringe at a 90 degree angle with the needle in its deeply imbedded position. Grasp the barrel of the syringe firmly with one hand. With the other hand, pull back the plunger and aspirate for several seconds to ensure that no blood appears. If any blood is drawn into the syringe, immediately withdraw and discard the syringe and prepare another dose.

If no blood is aspirated, reinforce the current needle position to avoid any movement of the needle and slowly (over 60 to 90 seconds) depress the plunger carefully and at a constant rate, until all the medication has been delivered. Be sure to depress the plunger completely with sufficient controlled force. Withdraw the needle. Immediately upon removal of the needle from the muscle, apply gentle pressure with a sterile pad to the injection site. If there is bleeding at the injection site, apply a bandage.

Following each injection of testosterone decanoate, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious pulmonary oil microembolism reactions or anaphylaxis.

Contraindications

The use of T-HIM Depot Injection is contraindicated in men with the following:

- 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.

The use of T-HIM Depot Injection in women is contraindicated. Testosterone can cause fetal harm when administered to a pregnant woman. It may cause serious adverse reactions in nursing infants. Exposure to androgens in both these cases may result in varying degrees of virilization.

Warnings And Precautions

- Drug Interactions

**Insulin**
Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication.

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

**Corticosteroids**
The concurrent use of corticosteroids may result in increased fluid retention and requires careful monitoring, particularly in patients with cardiac, renal or hepatic disease.

**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.

**Cardiac, Hepatic or Renal Insufficiency**
In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone should be used with caution. It 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.

**Pregnancy**
Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens, such as testosterone, may result in varying degrees of virilization. If this drug is used in pregnancy or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

T-HIM DEPOT INJECTION is not indicated for use in women and must not be used in pregnant women.

**Lactation**
Although it is not known how much testosterone transfers into human milk, T-HIM DEPOT INJECTION is not indicated for use in women and must not be used in breastfeeding women because of the potential for serious adverse effects in nursing infants.

**Fertility**
Testosterone replacement therapy may reversibly reduce spermatogenesis.

**Paediatric Use**
T-HIM DEPOT INJECTION is not indicated for use in children and adolescents, and it has not been clinically evaluated in males under 18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

**Geriatric Use**
Data are limited but do not suggest any increased risk of cardiovascular disease and prostate cancer or the need for a dosage adjustment in elderly patients. Geriatric patients treated with androgens may also be at risk for worsening of
signs and symptoms of BPH.

### Elderly Population

There is limited experience on the safety and efficacy of the use of testosterone undecanoate 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.

### General

T-HIM Depot Injection is not recommended for use in children and adolescents.

T-HIM Depot Injection 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.

### Medical Examinations 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 prostate-specific antigen) 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.

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.

T-HIM Depot Injection 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 T-HIM Depot Injection, a liver tumour should be included in the differential-diagnostic considerations.

### Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

Patients with BPH treated with androgens are at an increased risk of worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.

Patients treated with androgens may be at an increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens.
Serious POME reactions, involving cough, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate 1000 mg (4 mL). The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization. To minimize the risk of intravascular injection of T-HIM Depot Injection, care should be taken to inject the preparation deeply into the gluteal muscle, being sure to follow the recommended procedure for intramuscular administration. In addition to serious POME reactions, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate.

Both serious POME reactions and anaphylaxis can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. Patients with suspected hypersensitivity reactions to T-HIM Depot Injection should not be re-treated with T-HIM Depot Injection.

Following each injection of T-HIM Depot Injection, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions and anaphylaxis.

### Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

### Venous Thromboembolism

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as T-HIM Depot Injection. Evaluate patients who report symptoms of pain, edema, 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 T-HIM Depot Injection and initiate appropriate workup and management.

### 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.

### Hypertension

Testosterone may cause a rise in blood pressure and T-HIM DEPOT INJECTION should be used with caution in men with hypertension. As a general rule, the limitations of using intramuscular injections in patients with acquired or inherited blood clotting irregularities always have to be observed.

### Other Conditions

T-HIM DEPOT INJECTION 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.
Certain clinical signs such as irritability, nervousness, weight gain, and 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 that 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. Testosterone undecanoate should be permanently withdrawn if symptoms of excessive androgen exposure persist or reappear during treatment with the recommended dosage regimen.

Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism.

Hypercalcemia

Androgens, including T-HIM Depot Injection, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

Decreased Thyroxine-binding Globulin

Androgens, including T-HIM Depot Injection, may decrease concentrations of thyroxine-binding globulin, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Lipids

Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy.

Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic steroids. Anabolic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions. If 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 and anabolic androgenic steroids. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, T-HIM Depot injection is not indicated for use in women.

Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g. methyltestosterone) has been associated with
serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (e.g. jaundice). If these occur, promptly discontinue T-HIM depot injection while the cause is evaluated.

**Sleep Apnea**

The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

**Edema**

Androgens may promote retention of sodium and water. Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

**Cardiovascular Risk**

Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized 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 testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or continue to use T-HIM Depot injection.

**Renal Impairment**

No studies were conducted in patients with renal impairment.

**Hepatic Impairment**

No studies were conducted in patients with hepatic impairment.

**Drug Abuse and Dependence**

**Controlled Substance**

T-HIM Depot Injection contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

**Abuse**

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse of men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

**Abuse-Related Adverse Reactions**

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice,
clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities. The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty. Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dependence

**Behaviors Associated with Addiction**

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

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

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug.

Individuals taking supratherapeutic doses of 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. Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

**Undesirable Effects**

**Clinical Trial Experience**

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

Pulmonary microembolism of oily solutions can, in rare cases, lead to signs and symptoms such as cough, dyspnoea, throat tightening, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible and mostly resolvable with supportive measures. However, some lasted for up to a few hours and some required emergency care and/or hospitalization. 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.

**Suspected anaphylactic reactions after testosterone undecanoate 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 testosterone undecanoate. 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 six clinical studies (N=422) and considered at least, possibly, causally related to testosterone undecanoate.

Tabulated List of ADRs

**Table 1: Categorized 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 intramuscular injections of 4 ml, and N=120 with 3 ml of TU 250 mg/ml**
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<th>System Organ Class</th>
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<th>Uncommon</th>
<th>Rare</th>
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<td>Gastrointestinal disorders</td>
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<td>Nausea</td>
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<td>Aspartate aminotransferase increased</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Acne</td>
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<td>Erythema</td>
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<td>Rash¹</td>
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<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
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<td>Blood creatine phosphokinase increased</td>
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<td>Reproductive system and breast disorders</td>
<td>PSA increased</td>
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<td>Prostate examination abnormal</td>
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<td>Benign prostate hyperplasia</td>
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<td>Prostatic intraepithelial neoplasia</td>
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<td>Libido changes</td>
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<td>Gynaecomastia</td>
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### General disorders and administration site conditions
- Various kinds of injection site reactions
  - Rash including rash papular
  - Muscle disorders: muscle spasm, muscle strain and myalgia
  - Various kinds of injection-site reactions: Injection-site pain, injection-site discomfort, injection-site pruritus, injection-site erythema, injection-site haematoma, injection-site irritation, injection-site reaction
- Fatigue
- Asthenia
- Hyperhidrosis

### 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 disorders: muscle spasm, muscle strain and myalgia
3 Various kinds of injection-site reactions: 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

## Postmarketing

The following adverse reactions have been identified during post-approval use of testosterone undecanoate. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Pulmonary Oil Microembolism (POME) and Anaphylaxis

Serious pulmonary oil microembolism (POME) reactions, involving cough, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate 1000 mg (4 mL) in post-approval use outside the United States. The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization. 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.

In addition to serious POME reactions, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate in post-approval use outside of the United States.

In addition to the above-mentioned ADRs, 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 during treatment with testosterone-containing preparations, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate in post-approval use outside of the United States.

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-dose or long-term administration of testosterone occasionally increases the occurrence of water retention and oedema.

The following treatment emergent adverse events or adverse reactions have been identified during post-marketing
clinical trials and during post-approval use of intramuscular testosterone undecanoate. In most cases, the dose being used was 1000 mg.

**Blood and Lymphatic System Disorders**: polycythemia, thrombocytopenia

**Cardiac Disorders**: angina pectoris, cardiac arrest, cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, tachycardia

**Ear and Labyrinth Disorders**: sudden hearing loss, tinnitus

**Endocrine Disorders**: hyperparathyroidism, hypoglycemia

**Gastrointestinal Disorders**: abdominal pain upper, diarrhea, vomiting

**General Disorders and Administrative Site Conditions**: chest pain, edema peripheral, injection site discomfort, injection site hematoma, injection site irritation, injection site pain, injection site reaction, malaise, paresthesia, procedural pain

**Immune System Disorders**: anaphylactic reaction, anaphylactic shock, asthma, dermatitis allergic, hypersensitivity, leukocytoclastic vasculitis

**Infections and Infestations**: injection site abscess, prostate infection

**Investigations**: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood glucose increased, blood pressure increased, blood prolactin increased, blood testosterone decreased, blood testosterone increased, blood triglycerides increased, gamma-glutamyltransferase increased, hematocrit increased, intraocular pressure increased, liver function test abnormal, prostate examination abnormal, prostatic specific antigen increased, transaminases increased

**Metabolism and Nutrition Disorders**: diabetes mellitus, fluid retention, hyperlipidemia, hypertriglyceridemia

**Musculoskeletal and Connective Tissue Disorders**: musculoskeletal chest pain, musculoskeletal pain, myalgia, osteopenia, osteoporosis, systemic lupus erythematosus

**Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)**: prostate cancer, prostatic intraepithelial neoplasia

**Nervous System Disorders**: stroke, cerebrovascular insufficiency, reversible ischemic neurological deficiency, transient ischemic attack

**Psychiatric Disorders**: aggression, anxiety, depression, insomnia, irritability, Korsakoff’s psychosis non-alcoholic, male orgasmic disorder, nervousness, restlessness, sleep disorder

**Renal and Urinary Disorders**: calculus urinary, dysuria, hematuria, nephrolithiasis, pollakiuria, renal colic, renal pain, urinary tract disorder

**Reproductive System and Breast Disorders**: azoospermia, benign prostatic hyperplasia, breast induration, breast pain, erectile dysfunction, gynecomastia, libido decreased, libido increased, prostate induction, prostatitis, spermatocele, testicular pain

**Respiratory, Thoracic and Mediastinal Disorders**: asthma, chronic obstructive pulmonary disease, cough, dysphonia, dyspnea, hyperventilation, obstructive airway disorder, pharyngeal edema, pharyngolaryngial pain, pulmonary microemboli, pulmonary embolism, respiratory distress, rhinitis, sleep apnea syndrome, snoring

**Skin and Subcutaneous Tissue Disorders**: acne, alopecia, angioedema, angioneurotic edema, dermatitis allergic, erythema, hiperhidrosis, pruritus, rash

**Vascular Disorders**: cerebral infarction, cerebrovascular accident, circulatory collapse, deep venous thrombosis, hot flush, hypertension, syncope, thromboembolism, thrombosis, venous insufficiency

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side effects you can help provide more information on the safety of this product.
Overdosage

There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident. No special therapeutic measure apart from termination of therapy with the medicinal product or dose reduction is necessary after overdose along with appropriate symptomatic and supportive care.

Incompatibility

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

Storage And Handling Instructions

Store in a cool, dry place. Protect from light.

Packaging Information

T-HIM Depot Injection: Available as 4 ml Vial.

Last updated: October 2018
Last reviewed: October 2018

T-HIM Depot Injection

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