PRODUCT MONOGRAPH

◈ DEPO-TESTOSTERONE

testosterone cypionate injection

100 mg/mL sterile solution

USP

Androgens

Pfizer Canada ULC
17, 300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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DEPO-TESTOSTERONE

testosterone cypionate injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	Sterile injection, 100 mg/mL	benzyl alcohol, benzyl benzoate, cottonseed oil *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DEPO-TESTOSTERONE (testosterone cypionate injection) is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism).

DEPO-TESTOSTERONE (testosterone cypionate injection) should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other etiologies responsible for the symptoms have not been excluded. Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by two separate validated biochemical assays (morning testosterone) before initiating therapy with any testosterone replacement, including DEPO-TESTOSTERONE treatment.

Safety and efficacy of Depo-Testosterone (testosterone cypionate injection) in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.

Geriatrics (> 65 years of age):
There are no controlled clinical trial data to support the use of DEPO-TESTOSTERONE in the geriatric population (see **WARNINGS AND PRECAUTIONS – Special Populations, Geriatrics**, and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age):
DEPO-TESTOSTERONE is not indicated for use in children < 18 years of age since safety and efficacy have not been established in this patient population (see **WARNINGS AND PRECAUTIONS – Special Populations, Pediatrics**).

CONTRAINDICATIONS

DEPO-TESTOSTERONE is not indicated for use in women, especially during pregnancy as its use is known to cause virilization of the external genitalia of the female fetus (see **WARNINGS AND PRECAUTIONS – Special Populations).**

Androgens are contraindicated in men with known or suspected carcinoma of the prostate or breast.

DEPO-TESTOSTERONE should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone that is chemically synthesized from soy. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING.**

WARNINGS AND PRECAUTIONS

General

There are no controlled clinical trial data with testosterone cypionate injection in the geriatric male (> 65 years of age) to support the efficacy and safety of prolonged use. Impacts to prostate and cardiovascular event rates and patient important outcomes are unknown.

DEPO-TESTOSTERONE should not be used to attempt to enhance athletic performance, or alter body composition. Efficacy and safety of DEPO-TESTOSTERONE use for such purposes have not been established. Patients should be counselled concerning the serious long-term deleterious health issues that are associated with testosterone and anabolic steroid abuse. (See **WARNINGS AND PRECAUTIONS; Addiction, Abuse, Misuse** and also **WARNINGS AND PRECAUTIONS; Dependence**)

If testosterone deficiency has not been established, testosterone replacement therapy should not be used for the treatment of sexual dysfunction.

Clinical studies have not established testosterone replacement therapy as a treatment for male infertility.

DEPO-TESTOSTERONE contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Premature and low-birth weight infants may be more likely to develop toxicity.

Testosterone cypionate should not be used interchangeably with testosterone propionate because of differences in the duration of action.

Addiction, Abuse and Misuse

DEPO-TESTOSTERONE contains testosterone, a Schedule G controlled substance as defined by the Food and Drugs Act.

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 adverse effects, including psychiatric effects and effects on the cardiovascular system, which may be fatal (see **OVERDOSAGE, Chronic overdosage caused by abuse**).

If testosterone abuse is suspected, serum testosterone concentrations should be checked to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives.

Carcinogenesis and Mutagenesis
Please see also **TOXICOLOGY, Human Data.**

Prostatic: Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma (see **Special Populations – Geriatrics**).

Breast: Patients using long-term testosterone replacement therapy may be at an increased risk for the development of breast cancer.

Hepatic: Prolonged use of high doses of orally active 17-α alkyl-androgens (e.g. methyltestosterone) has been associated with serious hepatic effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular administration of testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas.

Skeletal: Patients with skeletal metastases are at risk of exacerbating hypercalcemia/hypercalciuria with concomitant androgen therapy.

Cardiovascular
Testosterone may increase blood pressure and should be used with caution in patients with hypertension.

Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease. Diuretic therapy may be required, in addition to discontinuation of the drug.

Some post-market studies suggest increased risk of serious cardiovascular events such as myocardial infarction and stroke associated with testosterone therapy. Patients should be informed of this possible risk when deciding whether to use or to continue to use Depo-Testosterone (testosterone cypionate injection). Before starting testosterone therapy, patients should be assessed for any cardiovascular risk factors (e.g. existing ischaemic heart disease) or prior history of cardiovascular events (e.g. myocardial infarction, stroke, or heart failure). Patients should also be closely monitored for possible serious cardiovascular events while on testosterone therapy. If any of these serious adverse events are suspected, treatment with Depo-Testosterone should be discontinued and appropriate assessment and management initiated.

Dependence
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.

Endocrine and Metabolism
Androgens have been shown to alter glucose tolerance tests. Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly (see **DRUG INTERACTIONS - Drug-Drug Interactions**).

Hypercalciuria/hypercalcemia (caused by malignant tumours) may be exacerbated by androgen treatment. Androgens should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in patients at risk of hypercalciuria/hypercalcemia.

Hypercalcemia may occur in immobilized patients. If this occurs, the drug should be discontinued.

Hematologic
Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy (see **Monitoring and Laboratory Tests**).

Alkylated derivatives of testosterone such as methandrostenolone, have been reported to decrease the anticoagulant requirement of patients receiving oral anticoagulants (e.g. warfarin). Patients receiving oral anticoagulant therapy require close monitoring, especially when androgens are started or stopped (see **DRUG INTERACTIONS - Drug-Drug Interactions**).

Ophthalmologic
Testosterone treatment can cause chorioretinopathy. Chorioretinopathy can lead to visual disturbances.

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

Sexual Function/Reproduction
Gynecomastia may frequently develop and occasionally persists in patients being treated for hypogonadism.

Priapism or excessive sexual stimulation may develop.

Oligospermia may occur after prolonged administration or excessive dosage.

Skin
Inflammation and pain at the site of intramuscular injection may occur.

Special Populations
Pregnant Women: DEPO-TESTOSTERONE should not be used in pregnant women. Benzyl alcohol can cross the placenta. (see **WARNINGS AND PRECAUTIONS, General**).
Testosterone may cause fetal harm. Testosterone exposure during pregnancy has been reported to be associated with fetal abnormalities. Testosterone is known to cause virilization of the external genitalia of the female fetus when administrated to pregnant women.

Nursing Women: DEPO-TESTOSTERONE should not be used in nursing women.

Pediatrics (< 18 years of age): Androgen therapy should be used cautiously in males with hypogonadism causing delayed puberty. Androgens can accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater risk of compromising final mature height. The effect of androgens on bone maturation should be monitored closely by assessing bone age of the wrist and hand on a regular basis.

Geriatrics (> 65 years of age): There are very limited controlled clinical study data supporting the use of testosterone in the geriatric population and virtually no controlled clinical studies on subjects aged 75 years and over.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy.

In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men.

Monitoring and Laboratory Tests
Prior to initiating Depo-Testosterone, baseline testosterone levels should be appropriately assessed (see DOSAGE AND ADMINISTRATION, Dosing Considerations). The patients should be monitored (including serum testosterone levels) on a regular basis to ensure adequate response to treatment.

Currently there is no consensus about age specific testosterone levels. The normal serum testosterone level for young eugonadal men is generally accepted to be approximately 10.4 - 34.6 nmol/L (300-1000 ng/dL). However, it should be taken into account that physiological testosterone levels are lower with increasing age.
The following laboratory tests, performed routinely, are recommended to ensure that adverse effects possibly caused by or related to testosterone replacement therapy is detected and addressed:

- hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia);
- liver function tests; to detect hepatotoxicity associated with the use of 17-alpha-alkylated androgens;
- prostate specific antigen (PSA) levels, Digital Rectal Examination (DRE), especially if the patient presents with progressive difficulty with urination or a change in voiding habits;
- lipid profile, total cholesterol, LDL, HDL, and triglycerides;
- diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly (see **DRUG INTERACTIONS - Drug-Drug Interactions**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following adverse reactions in the male have occurred with some androgens:

Table 1: Adverse Drug Reactions Associated with the Use of Androgen Therapy

MedDRA System Organ Class (SOC)	Adverse Drug Reaction
Blood and the lymphatic system disorders:	Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.
Cardiovascular disorders:	Myocardial infarction, stroke
Gastrointestinal disorders:	Nausea
General disorders and administration site conditions:	Inflammation and pain at the site of intramuscular injection.
Hepatobiliary disorders:	Cholestatic jaundice, alterations in liver function tests, hepatocellular neoplasms and peliosis hepatis
Immune system disorders:	Hypersensitivity, including skin manifestations and anaphylactoid reactions.
Metabolism and nutrition disorders:	Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.
Nervous system disorders:	Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.
Reproductive system and breast disorders:	Gynecomastia, excessive frequency and duration of penile erections, and oligospermia.
Skin and subcutaneous tissue disorders:	Hirsutism, male pattern of baldness, seborrhea, and acne.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing use of testosterone replacement therapy in general. Because these 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.

Table 2: Adverse Drug Reactions from Post-marketing Experience of Testosterone Replacement Therapy:

MedDRA System Organ Class (SOC)	Adverse Drug Reaction
Blood and the lymphatic system disorders:	Erythropoiesis abnormal
Cardiovascular disorders:	Tachycardia, atrial fibrillation, pulmonary embolism, and deep vein thrombosis
Endocrine disorders:	Abnormal accelerated growth
Eye disorders:	Chorioretinopathy
Gastrointestinal disorders:	Vomiting, diarrhea, abdominal pain, gastrointestinal bleeding
General disorders and administration site conditions:	Edema, malaise, fatigue, application site burning, application site induration, application site rash, application site dermatitis, application site blister, application site erythema
Investigations:	Weight increase, fluctuating testosterone levels, testosterone decreased, lipids abnormalities
Metabolism and nutrition disorders:	Increased appetite, urine calcium decrease, glucose tolerance impaired, elevated cholesterol
Musculoskeletal and connective tissue disorders:	Myalgia, arthralgia
Nervous system disorders:	Insomnia, headache, dizziness
Psychiatric disorders:	Personality disorder, confusion, anger, aggression, cognitive disturbance
Renal and urinary disorders:	Dysuria, hematuria, incontinence, bladder irritability
Reproductive system and breast disorders:	Prostate carcinoma, enlarged prostate (benign), free prostate-specific antigen increased, testicular atrophy, epdidymitis, priapism, impotence, precocious puberty, mastodynia
Respiratory, thoracic and mediastinal disorders:	Dyspnea, sleep apnea
Skin and subcutaneous tissue disorders:	Pruritus, rash, urticaria, vesiculo-bullous rash, alopecia
Vascular disorders:	Hypertension

DRUG INTERACTIONS

Drug-Drug Interactions

Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Propranolol: In a published pharmacokinetic study of an injectable testosterone product, administration of testosterone cypionate led to an increased clearance of propranolol in the majority of men tested.

Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus these drugs should be administered cautiously particularly in patients with cardiac, renal or hepatic disease.

Anticoagulants: Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore may decrease plasma testosterone levels.

Drug-Laboratory Test Interactions
Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Prior to initiating DEPO-TESTOSTERONE (testosterone cypionate injection), the diagnosis of hypogonadism should be confirmed 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. Testosterone levels should then be monitored on a regular basis to ensure adequate response to treatment (See Monitoring and Laboratory Tests). DEPO-TESTOSTERONE should be used only in patients available for re-evaluation at periodic intervals.

DEPO-TESTOSTERONE is to be administered by a health care professional only.

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

Dosage should be adjusted according to the patient's response and appearance of adverse reactions.

Recommended Dose and Dosage Adjustment
For replacement in the hypogonadal male, 200 mg should be administered every two weeks.
Maximum Dose: 400 mg per month.

Missed Dose
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

Administration
Parenteral drug products, such as DEPO-TESTOSTERONE, should be inspected visually for particulate matter and discolouration prior to administration. Warming and shaking the vial should redissolve any crystals that may have formed during storage.

OVERDOSAGE

Acute overdosage
Symptoms of an acute testosterone overdose are not known. No specific antidote is available. Symptomatic and supportive treatment should be given.

Chronic overdosage caused by abuse
Testosterone, often in combination with other anabolic androgenic steroids (AAS), has been subject to abuse at doses higher than recommended for the approved indication. Serious and even fatal adverse reactions have been reported in individuals who abuse anabolic androgenic steroids.

Some of the adverse reactions associated with chronic AAS overdosage are an extension of the adverse reactions associated with testosterone use within the therapeutic range. However, other adverse events may be the opposite of what is expected when used therapeutically. Some of the exacerbated, new or opposite adverse events associated with chronic AAS overdosage include:

Cardiovascular: cardiac arrest, hypertrophic cardiomyopathy, cerebrovascular accident, transient ischemic attacks, dyslipidemias.
CNS/Psychiatric: convulsions, serious psychiatric manifestations (including major depression, mania, hypomania, paranoia, psychosis, delusions, hallucinations and hostility).
Female reproductive system: clitoral enlargement, breast atrophy and menstrual irregularities.
Liver: hepatotoxicity
Male reproductive system: subfertility and infertility.
Other: virilization, deepening of voice (which may be permanent in women), premature closure of bony epiphyses with termination of growth in children/adolescents and precocious puberty.

Individuals who have taken supratherapeutic doses of testosterone may experience withdrawal symptoms upon discontinuation (see **WARNINGS AND PRECAUTIONS, Dependence**).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action:

DEPO-TESTOSTERONE delivers testosterone in the form of testosterone cypionate intramuscularly to produce circulating testosterone levels that approximate normal levels (e.g. 10.4 – 34.6 nmol/L [300 - 1000 ng/dL]) seen in healthy young men.

Pharmacodynamics

Testosterone and Hypogonadism: Testosterone and dihydrotestosterone (DHT), endogenous androgens, are responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis. Hypogonadism is a risk factor for osteoporosis in men.

General Androgen Effects: Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium.

Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process.

During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Pharmacokinetics

Absorption: Testosterone cypionate is a testosterone ester. Esterification of testosterone at position 17 increases the lipid solubility of the testosterone molecule and prolongs the activity of the molecule by increasing its residence time. Following intramuscular administration in an oily vehicle, testosterone ester is slowly absorbed into the general circulation and then rapidly hydrolysed in plasma to testosterone.
In a randomized cross-over study of six healthy males aged 20-29 years of age, the pharmacokinetics of a single injection of 200 mg testosterone cypionate was compared to that of

a single injection of 194 mg testosterone enanthate. Mean serum testosterone concentrations increased sharply to 3 times the basal levels (approximately 1350 ng/dL) at 24 hours and declined gradually to basal levels (approximately 500 ng/dL) by day 10.

A similar observation was noted in a clinical study of replacement therapy with a single intramuscular dose of 200 mg testosterone cypionate in 11 hypogonadal males aged 28-74. Pharmacokinetic analysis showed a three-fold mean increase in serum testosterone concentrations by day 2 (1108 ± 440 ng/dL) and a progressive decline to basal serum levels (360 ± 166 ng/dL) by day 14 for the group.

These pharmacokinetic studies demonstrated the dosing regimen of 200 mg testosterone cypionate every 2 weeks led to initial elevation of serum testosterone into the supraphysiological range and then a gradual decline into the hypogonadal range by the end of the dosing interval.

Distribution: Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen.

Metabolism: There is considerable variation in the half-life of testosterone as reported in the literature, ranging from ten to 100 minutes.

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). Testosterone is metabolized to DHT by steroid 5α-reductase located in the skin, liver, and the urogenital tract of the male. Estradiol is formed by an aromatase enzyme complex in the brain, fat, and testes. DHT binds with greater affinity to SHBG than does testosterone. In many tissues, the activity of testosterone depends on its reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action. In reproductive tissues, DHT is further metabolized to 3-α and 3-β androstanediol.

Excretion: About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

STORAGE AND STABILITY

Store at room temperature (15°C - 30°C). **Protect from light**.

SPECIAL HANDLING INSTRUCTIONS

Proper disposal of needles and syringes: All used injection equipment must be safely disposed according to local environmental health regulations. All disposable syringes and needles should be disposed immediately following use in a designated safety box or puncture-proof container. Treatment materials and waste should be stored and disposed appropriately to reduce dangers to others.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DEPO-TESTOSTERONE is available in one strength, 100 mg testosterone cypionate /mL.

DEPO-TESTOSTERONE is available in the following packaging: **100 mg per mL** – In vials of 10 mL.

Each mL of the 100 mg/mL DEPO-TESTOSTERONE solution contains:

Testosterone cypionate	100 mg
Benzyl alcohol	9 mg
Benzyl benzoate	0.1 mL
Cottonseed oil	q.s.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

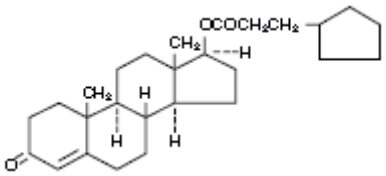
Drug Substance

Proper name: testosterone cypionate

Chemical name: androst-4-en-3-one,17-(3-cyclopentyl-1-oxopropoxy)-, (17ß)

Molecular formula and molecular mass: $C_{27}H_{40}O_3$ and 412.61

Structural formula:



Physicochemical properties: Testosterone cypionate is the oil-soluble 17ß-cyclopentylpropionate ester of testosterone. Testosterone is a white or creamy white crystalline powder, odourless or nearly so and stable in air. It is insoluble in water, freely soluble in alcohol, chloroform, dioxane, ether, and in vegetable oils.

CLINICAL TRIALS

There are no available pivotal clinical trial data for DEPO-TESTOSTERONE (testosterone cypionate injection USP), although clinical studies have been conducted with other testosterone formulations.

TOXICOLOGY

Animal data

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically- induced carcinomas of the liver in rats.

Human data

There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

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PART III: CONSUMER INFORMATION

DEPO-TESTOSTERONE
Testosterone cypionate injection USP

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DEPO-TESTOSTERONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed DEPO-TESTOSTERONE because your body is not making enough testosterone. The medical term for this condition is hypogonadism.

What it does:
DEPO-TESTOSTERONE delivers testosterone into the bloodstream through an injection into your gluteal muscle. DEPO-TESTOSTERONE helps raise your testosterone to normal levels.

When it should not be used:
- if you have prostate or breast cancer (confirmed or suspected by your doctor);
- if you have difficulty in urinating due to an enlarged prostate;
- if you have a known allergy or sensitivities to any of the ingredients contained in DEPO-TESTOSTERONE, including testosterone USP that is chemically synthesized from soy (see "What the medicinal and nonmedicinal ingredients are" in this section).

DEPO-TESTOSTERONE should **NOT** be used **by women**. Pregnant and breast feeding women are especially at risk. Testosterone may cause harm to your unborn baby.

What the medicinal ingredient is:
Testosterone cypionate

What the nonmedicinal ingredients are:
Benzyl alcohol, benzyl benzoate, and cottonseed oil

What dosage forms it comes in:
DEPO-TESTOSTERONE is available in one strength, 100 mg testosterone cypionate /mL.

DEPO-TESTOSTERONE is available in the following packaging: 100 mg per mL – In vials of 10 mL.

WARNINGS AND PRECAUTIONS

There is very little information from clinical trials with testosterone in the older male (>65 years of age) to support safe use for a long period of time.

DEPO-TESTOSTERONE is not recommended for use in children < 18 years of age.

DEPO-TESTOSTERONE can cause changes in your vision. It is called chorioretinopathy.

You should not use testosterone in an attempt to reduce weight and increase muscle, or improve athletic performance as it may cause serious health problems.

You should not use testosterone to treat sexual dysfunction or male infertility.

DEPO-TESTOSTERONE contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome" (difficulty in catching breath, low blood pressure, slow heart rate), and death in pediatric patients. Premature and low-birth weight infants may be more likely to develop toxicity.

Pregnancy: Benzyl alcohol can cross the placenta.

Before using DEPO-TESTOSTERONE, talk to your doctor if you:
- have difficulty urinating due to an enlarged prostate. Older patients may have a higher risk of developing an enlarged prostate or prostate cancer;
- have prostate cancer (confirmed or suspected);
- have liver, kidney or heart disease;
- have high blood pressure (hypertension);
- have diabetes;
- have breathing problems during sleep (sleep apnea);
- have heart or blood vessels problems or a history of these problems such as heart attack, stroke, or blood clots in the lungs or the legs.

Drug Abuse and Dependence: DEPO-TESTOSTERONE contains testosterone. Testosterone is a controlled substance because some people take it in high doses (abuse it), even if their body is making enough testosterone. Taking too much (abusing) testosterone can cause serious health problems, which can even lead to death (see **Overdose**).

Individuals who have abused testosterone may experience withdrawal symptoms lasting for weeks or months which include, but are not limited to: changes in mood, and appetite, as well as fatigue, insomnia, decreased sex drive and loss of function of the testes and ovaries.

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

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription.

Drugs that include:
- Insulin
- Corticosteroids
- Propranolol
- Warfarin

PROPER USE OF THIS MEDICATION

DEPO-TESTOSTERONE should only be administered by a health care professional.

When you are given DEPO-TESTOSTERONE, your blood testosterone should be checked on a regular basis.

Usual dose:
200 mg is given intramuscularly (in the muscle) every two weeks.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms

Taking too much (abusing) testosterone for a long time can cause serious health problems, which can even lead to death. Some of the health problems include effects on the cardiovascular system, reproductive system and the liver, as well as serious psychiatric problems.

Missed Dose:
If you have missed a dose of DEPO-TESTOSTERONE, you should contact your doctor to schedule your next injection.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DEPO-TESTOSTERONE can have side effects. The following side effects have been reported for testosterone products:
- skin irritation or redness or rash at the application site;
- increased prostatic specific antigen (PSA);
- enlarged prostate (benign prostatic hyperplasia);
- an increase in red blood cell count, (hematocrit and hemoglobin);
- acne;
- change in mood, depression;
- prolonged or painful erection;
- sleep disturbances caused by breathing problems;
- aggression or aggressive behaviour;
- breast enlargement and breast pain;
- loss of hair and baldness;
- high blood pressure;
- weight gain;
- headache, dizziness;
- increased or irregular heart rate, blood clot in the lungs or the legs;

This is not a complete list of side effects. For any unexpected effects while taking DEPO-TESTOSTERONE, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Urinary symptoms (i.e. change in frequency /color, dribbling, pain on urination, straining, weak stream, small amounts)		√	
Common (after prolonged use)	Breast enlargement or breast pain		√	
Uncommon	Swelling of ankles and legs (in patients with heart, kidney or liver damage)			√
Uncommon	Erections that are too frequent or continue for too long, or are painful.		√	
Uncommon	Liver problems, with symptoms such as nausea, vomiting, along with yellowed or darkened skin			√
Uncommon	**Heart Attack:** Crushing chest pain or heaviness, sharp pain in the chest, coughing blood, or sudden shortness of breath			√
Uncommon	**Stroke:** Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg			√
Unknown	**Chorioretinopathy:** blurred vision, blind spot, objects seeming smaller or distortion of straight lines		√	

HOW TO STORE IT

Store DEPO-TESTOSTERONE at controlled room temperature (15°C-30°C). Protect from light.

Keep in a safe place out of reach of children and pets.

You should not use your medication after the expiration date printed on the carton and label.

Keep all medications out of the reach of children. This medication could harm them.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

  - Fax toll-free to 1-866-678-6789, or

  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.
NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full prescribing information, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada ULC, at:
1-800-463-6001.

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