

## Testosterone Gel HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use testosterone gel safely and effectively. See full prescribing information for testosterone gel.

Testosterone gel for topical use CIII  
Initial U.S. Approval: 1953

### WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- Virilization has been reported in children who were secondarily exposed to testosterone gel. (5.2, 6.2)
- Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel. (2.2, 5.2)
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use. (2.2, 5.2, 17)

### RECENT MAJOR CHANGES

Warnings and Precautions (5.6) 12/2016

### INDICATIONS AND USAGE

Testosterone gel is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired). (1)
- Hypogonadotropic hypogonadism (congenital or acquired). (1)

Limitations of use:

- Safety and efficacy of testosterone gel in men with "age-related hypogonadism" have not been established. (1)
- Safety and efficacy of testosterone gel in males <18 years old have not been established. (8.4)

### DOSAGE AND ADMINISTRATION

- Prior to initiating testosterone gel, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range. (2)
- Starting dose of testosterone gel is 40 mg of testosterone (4 pump actuations) applied topically once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of the thighs. Do not apply testosterone gel to the genitals or other parts of the body. (2.2)
- Dose adjustment: testosterone gel can be dose adjusted between a minimum of 10 mg of testosterone (1 pump actuation) and a maximum of 70 mg of testosterone (7 pump actuations) on the basis of total serum testosterone concentrations 2 hours post testosterone gel application. The dose should be titrated based on the serum testosterone concentration from a single blood draw 2 hours after applying testosterone gel at approximately 14 days and 35 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter. (2.1)
- Patients should wash hands immediately with soap and water after applying testosterone gel and cover the application site with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)
- Testosterone gel is not interchangeable with other topical testosterone products. (2.1)

### DOSAGE FORMS AND STRENGTHS

- Testosterone gel is supplied as a metered-dose pump. One pump actuation delivers 10 mg of testosterone. (3)

### CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected prostate cancer. (4, 5.1)
- Pregnant or breastfeeding women. Testosterone may cause fetal harm. (4, 8.1, 8.3)

### WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to testosterone gel. Secondary exposure to testosterone can produce signs of virilization. Testosterone gel should be discontinued until the cause of virilization is identified. (5.2)
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.5)
- Exogenous administration of androgens may lead to azoospermia. (5.8)
- Edema with or without congestive heart failure (CHF) may be a complication in patients with pre-existing cardiac, renal, or hepatic disease. (5.10)
- Sleep apnea may occur in those with risk factors. (5.12)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically. (5.1, 5.3, 5.9, 5.13)
- Testosterone gel is flammable until dry. (5.16)

### ADVERSE REACTIONS

The most common adverse reaction (incidence  $\geq 3\%$ ) is skin reactions at the application site (16.1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients. (7.1)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended. (7.2)
- Use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal or hepatic disease. (7.3)

### USE IN SPECIFIC POPULATIONS

- There are insufficient long-term safety data in geriatric patients using testosterone gel to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved Medication Guide

Revised: 07/2017

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* Sections or subsections omitted from the full prescribing information are not listed.
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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- Virilization has been reported in children who were secondarily exposed to testosterone gel [see Warnings and Precautions (5.2) and Adverse Reactions (6.2)].
- Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel [see Dosage and Administration (2.2) and Warnings and Precautions (5.2)].
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use [see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)].

Testosterone gel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) – testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol, heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired) – gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations but have gonadotropins in the normal or low range.

Limitations of use:

- Safety and efficacy of testosterone gel in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- Safety and efficacy of testosterone gel in males <18 years old have not been established [see Use in Specific Populations (8.4)].

### 2 DOSAGE AND ADMINISTRATION

Prior to initiating testosterone gel 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.

#### 2.1 Dosing and Dose Adjustment

The recommended starting dose of testosterone gel is 40 mg of testosterone (4 pump actuations) applied once daily to the thighs in the morning. The dose can be adjusted between a minimum of 10 mg of testosterone and a maximum of 70 mg of testosterone. To ensure proper dosing, the dose should be titrated based on the serum testosterone concentration from a single blood draw 2 hours after applying testosterone gel at approximately 14 days and 35 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter. Table 1 describes the dose adjustments required at each titration step.

Table 1 - Dose Adjustment Criteria

Total Serum Testosterone Concentration 2 hours Post Testosterone Gel Application	Dose Titration
Equal to or greater than 2,500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1,250 and less than 2,500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1,250 ng/dL	No change: continue on current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)

The application site and dose of testosterone gel are not interchangeable with other topical testosterone products.

#### 2.2 Administration Instructions

Testosterone gel should be applied directly to clean, dry, intact skin of the front and inner thighs. Do not apply testosterone gel to the genitals or other parts of the body. Patients should be instructed to use one finger to gently rub testosterone gel evenly onto the front and inner area of each thigh as directed in Table 2.

Table 2 - Application of Testosterone Gel

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1
30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

Once the application site is dry, the site should be covered with clothing [see Clinical Pharmacology (12.3)]. Wash hands thoroughly with soap and water. Avoid applying the gel to the thigh adjacent to the scrotum. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including testosterone gel, are flammable.

The patient should avoid swimming or showering or washing the administration site for a minimum of 2 hours after application [see Clinical Pharmacology (12.3)].

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator eight times. The first three actuations may result in no discharge of gel. Safely discard the gel from the first eight actuations. It is only necessary to prime the pump before the first dose.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from testosterone gel-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using testosterone gel.
- Testosterone gel should only be applied to the front and inner thighs (area of application should be limited to the area that will be covered by the patient's shorts or pants).
- Patients should wash their hands immediately with soap and water after applying testosterone gel.
- Patients should cover the application site(s) with clothing (e.g., shorts of sufficient length or pants) after the gel has dried.
- Prior to any situation in which skin-to-skin contact with the application site is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which testosterone gel has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

### 3 DOSAGE FORMS AND STRENGTHS

Testosterone gel for topical use only, is supplied in a metered-dose pump. One pump actuation delivers 10 mg of testosterone.

### 4 CONTRAINDICATIONS

- Testosterone gel is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate [see Warnings and Precautions (5.1), Adverse Reactions (6.1)].
- Testosterone gel is contraindicated in women who are or may become pregnant, or who are breastfeeding. Testosterone gel may cause fetal harm when administered to a pregnant woman. Testosterone gel may cause serious adverse reactions in nursing infants. Exposure of a female fetus or nursing infant to androgens may result in varying degrees of virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with testosterone gel. If a pregnant woman is exposed to testosterone gel, she should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1, 8.3)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 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 increased risk for prostate cancer. Evaluation of the patients for the presence of prostate cancer prior to initiating and during treatment with androgens is appropriate [see Contraindications (4)].

#### 5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using testosterone gel [see Dosage and Administration (2.2), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)].

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to testosterone gel should also be brought to the attention of a physician. Testosterone gel should be promptly discontinued until the cause of virilization has been identified.

#### 5.3 Polycythemia

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

#### 5.4 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 testosterone gel. 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 testosterone gel and initiate appropriate workup and management.

#### 5.5 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 to continue to use testosterone gel.

#### 5.6 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 androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions [see Drug Abuse and Dependence (9)].

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 derivatives. 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.

#### 5.7 Use in Women

Due to the lack of controlled evaluations in women and potential virilizing effects, testosterone gel is not indicated for use in women [see Contraindications (4) and Use in Specific Populations (8.1, 8.3)].

#### 5.8 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including testosterone gel, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH which could possibly lead to adverse effects on semen parameters including sperm count.

#### 5.9 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 hepatis, hepatic neoplasms, cholestatic hepatitis and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate has produced multiple hepatic adenomas. Testosterone gel is not known to cause these adverse effects.

#### 5.10 Edema

Androgens, including testosterone gel, 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 [see Adverse Reactions (6.2)].

#### 5.11 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including testosterone gel, for hypogonadism.

#### 5.12 Sleep Apnea

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

#### 5.13 Lipids

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

#### 5.14 Hypercalcemia

Androgens, including testosterone gel, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalcaemia). Regular monitoring of serum calcium concentrations is recommended in these patients.

#### 5.15 Decreased Thyroxine-binding globulin

Androgens, including testosterone gel, may decrease concentrations of thyroxine-binding globulins, 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.

#### 5.16 Flammability

Alcohol based products, including testosterone gel, are flammable; therefore, patients should be advised to avoid smoking, fire or flame until the testosterone gel has dried.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a controlled multicentre, open label, non-comparative 90-day clinical study, 149 hypogonadal patients were treated with testosterone gel [see Clinical Studies (14.1)]. Adverse reactions occurred in 22.8% (34/149) of patients. The most common adverse reaction reported in this study was skin reactions associated with the site of application (16.1%; 24/149) of which 79% (19/24) were mild, and the remainder were moderate (21%; 5/24) (Table 3).

Table 3 - Adverse Reactions Reported in >1% Patients in the US Phase 3 Clinical Trial of Testosterone Gel

Adverse Reaction	Number (%) of Patients N = 149
Skin reaction	24 (16.1%)
Prostatic specific antigen increased	2 (1.3%)
Abnormal dreams	2 (1.3%)

During the 90 day trial 5 patients (3.4%) discontinued treatment because of adverse reactions. These reactions were: 1 patient with contact dermatitis (considered probably related to testosterone gel application), 1 with application site reaction (considered probably related to testosterone gel application), 1 with gastrointestinal hypomotility (considered possibly related to testosterone gel application), 1 with severe dyspnea (considered not related to testosterone gel application), and 1 with moderate cutaneous (considered not related to testosterone gel application).

#### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of testosterone gel. 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 4).



**Table 4 - Adverse Drug Reactions from Post approval Experience of Testosterone Gel by System Organ Class**

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders	Polycythemia
Eye disorders	Vitreous detachment
Gastrointestinal disorders	Abdominal symptoms
General disorders and administrative site conditions	Application site erythema, irritation, pruritus, and swelling; fatigue, influenza like illness, and malaise.
Investigations	Decreased serum testosterone, increased hematocrit and hemoglobin
Musculoskeletal and connective tissue disorders	Pain in extremity
Nervous system disorders	Dizziness, headache, and migraine
Reproductive system and breast disorders	Erectile dysfunction, and priapism
Skin and subcutaneous tissue disorders	Allergic dermatitis, erythema, rash, and papular rash.
Vascular disorders	Venous thromboembolism
Cardiovascular disorders	Myocardial infarction, stroke

**Secondary Exposure to Testosterone in Children**

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or the penis, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases with a reported outcome, these signs and symptoms were reported to have regressed with removal of the testosterone gel exposure. In a few cases, however, enlarged genitalia did not fully return to age appropriate normal size, and bone age remained modestly greater than chronological age. In some of the cases, direct contact with the sites of application on the skin of men using testosterone gel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the testosterone gel user's shirts and/or other fabric, such as towels and sheets [see *Warnings and Precautions (5.2)*].

**7 DRUG INTERACTIONS**

**7.1 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 decrease insulin requirements.

**7.2 Oral Anticoagulants**

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

**7.3 Corticosteroids**

The concurrent administration of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category X [see *Contraindications (4)*]. — Testosterone gel is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

**8.3 Nursing Mothers**

Although it is not known how much testosterone transfers into human milk, testosterone gel is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation [see *Contraindications (4)*].

**8.4 Pediatric Use**

The safety and efficacy of testosterone gel in pediatric patients <18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

**8.5 Geriatric Use**

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing testosterone gel to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 149 patients enrolled in the pivotal clinical study utilizing testosterone gel, 20 were over 65 years of age. Additionally, there are insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH.

**8.6 Renal Impairment**

No studies were conducted in patients with renal impairment.

**8.7 Hepatic Impairment**

No studies were conducted in patients with hepatic impairment.

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**

Testosterone gel contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

**9.2 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.

**9.3 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.

**10 OVERDOSAGE**

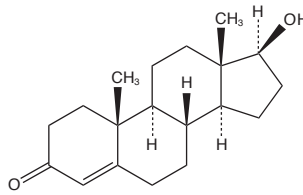
There is a single report of acute overdosage after parenteral administration of an approved testosterone product in the literature. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident. There were no reports of overdose in the testosterone gel clinical trial.

Treatment of overdosage would consist of discontinuation of testosterone gel, washing the application site with soap and water, and appropriate symptomatic and supportive care.

**11 DESCRIPTION**

Testosterone gel is a clear, colorless, odorless, gel containing testosterone. Testosterone gel is available in a metered-dose pump. Each pump actuation provides 10 mg of testosterone and each container is capable of dispensing 120 pump actuations. One pump actuation dispenses 0.5 g of gel.

The active pharmacologic ingredient in testosterone gel is testosterone. Testosterone USP is a white to almost white powder described chemically as 17-beta hydroxyandrost-4-en-3-one.



Pharmacologically inactive ingredients in testosterone gel are: propylene glycol, purified water, ethanol, 2-propanol, oleic acid, carbomer 1382, triethanolamine and butylated hydroxytoluene.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for the 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. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins (FSH, LH).

**12.2 Pharmacodynamics**

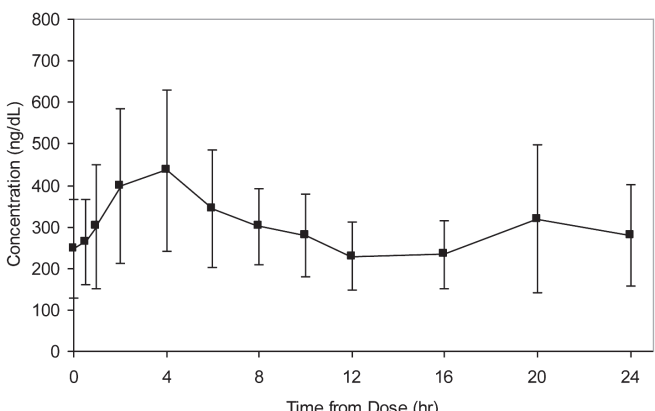
No specific pharmacodynamic studies were conducted using testosterone gel.

**12.3 Pharmacokinetics**

**Absorption**

Testosterone gel delivers physiologic amounts of testosterone, producing serum testosterone concentrations that approximate normal concentrations (> 300 ng/dL) seen in healthy men.

Testosterone gel provides continuous transdermal delivery of testosterone for 24 hours following a single application to clean, dry, intact skin of the front and inner thighs (Figure 1).



**Figure 1: Mean (±SD) Serum Total Testosterone Concentrations on Day 7 in Patients Following Testosterone Gel Once-Daily Application of 40 mg of Testosterone (N=12)**

**Distribution**  
Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins.

**Metabolism**

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

**Excretion**

There is considerable variation in the half-life of testosterone concentration as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulfuric acid conjugates of testosterone and its metabolites. About 6% is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

**Potential for testosterone transfer**

The potential for testosterone transfer from healthy males dosed with testosterone gel to healthy females was evaluated in a placebo-controlled, three-way crossover study. The washout period was approximately 29 days. Six males were treated with either testosterone gel (30 mg testosterone) or placebo to one thigh only. At 2 hours after the application of testosterone gel to males, the females rubbed their forearms for 15 minutes on the thigh of the males. Serum concentrations of testosterone were monitored in females for 24 hours after the transfer procedure. When direct skin-to-skin transfer occurred with testosterone gel mean C<sub>avg</sub> increased by 134% and mean C<sub>max</sub> increased by 191%, compared to direct skin-to-skin transfer with placebo. When transfer occurred with testosterone gel while covering a thigh with boxer shorts, mean C<sub>avg</sub> decreased by 3% and mean C<sub>max</sub> increased by 2%, compared to direct skin-to-skin transfer with placebo [see *Dosage and Administration (2.2)*].

**Effect of showering**

In a two-way crossover study, the effects of showering on the pharmacokinetics of total testosterone following application of testosterone gel (30 mg testosterone to each thigh; total 60 mg testosterone) were assessed in 7 hypogonadal males. There were two 7-day treatment phases, with showering 2 hours post testosterone gel application, and without showering on Day 7 of each treatment phase. Showering decreased C<sub>avg</sub> by 3% and it increased C<sub>max</sub> by 13% [see *Dosage and Administration (2.2)*].

**Effect of hand washing and application site (inner thigh) washing**

In an open-label, single-dose study, the amount of residual testosterone on the application finger and application site after washing was evaluated in 12 healthy male subjects. Prior to application of testosterone gel, each index finger and each intended application site (left and right front and inner thighs) was wiped using dry sponges to assess baseline skin testosterone. Subjects then used each index finger to rub testosterone gel (40 mg testosterone) onto each inner thigh. On one side, the index finger was immediately wiped using dry sponges to collect residual testosterone. On the other side, each subject washed their hands with liquid soap and warm tap water immediately after drug application, then wipe the index finger using dry sponges to collect residual testosterone. A mean (SD) of 0.002 (0.006) mg of residual testosterone (i.e., 99.8% reduction compared to when hand was not washed) was recovered after washing hands with liquid soap and warm tap water.

Two hours after the application of testosterone gel onto each inner thigh, one thigh was wiped using dry sponges. On the other thigh, the application site was washed with liquid soap and warm tap water, dried, and then wiped using dry sponges. The sponges were assayed for testosterone. A mean (SD) of 0.24 (0.009) mg of residual testosterone (i.e., 94.3% reduction compared to when application site was not washed) was recovered after application site washing.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, implant induced cervical-uterine tumors 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. Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

**14 CLINICAL STUDIES**

**14.1 Clinical Study in Hypogonadal Males**

Testosterone gel was evaluated in a multicenter, 90 day open-label, non-comparative trial of 149 hypogonadal males with body mass index (BMI) ≥ 22 kg/m<sup>2</sup> and < 35 kg/m<sup>2</sup> and 18-75 years of age (mean age 54.5 years). The patients were screened for a single serum total testosterone concentration < 250 ng/dL, or two consecutive serum total testosterone concentrations < 300 ng/dL. Patients were Caucasian (80.5%), Black (10.1%), Hispanic (7.4%) and other (2.0%).

Testosterone gel was applied once each morning to the thighs at a starting dose of 40 mg of testosterone (4 pump actuations) per day. The dose was adjusted between a minimum of 10 mg and a maximum of 70 mg testosterone on the basis of total serum testosterone concentration obtained 2 hours post testosterone gel application on Days 14, 35, and 60 (± 3 days).

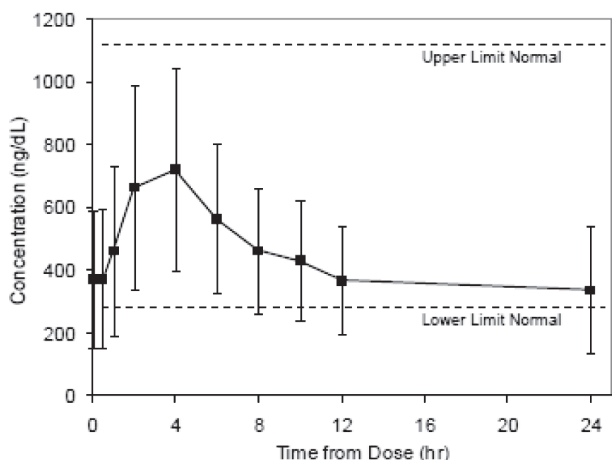
The primary endpoint was the percentage of patients with C<sub>avg</sub> within the normal range (greater than or equal to 300 ng/dL and less than or equal to 1140 ng/dL) on Day 90. In patients treated with testosterone gel, 77.5% (100/129) had C<sub>avg</sub> within the normal range on Day 90. The secondary endpoint was the percentage of patients with C<sub>max</sub> above three pre-determined limits. The percentages of patients with C<sub>max</sub> greater than 1500 ng/dL, and between 1800 and 2499 ng/dL on Day 90 were 5.4% and 1.6%, respectively. No patient had a C<sub>max</sub> greater than or equal to 2500 ng/dL on Day 90.

Dose titrations on Days 14, 35 and 60 resulted in mean (SD) C<sub>avg</sub> and C<sub>max</sub> for final doses of 10 mg - 70 mg on Day 90 shown in Table 5.

**Table 5 Mean (±SD) Steady-State Testosterone Concentrations (C<sub>avg</sub> and C<sub>max</sub>) by final dose on Day 90**

		Final Dose						
		10mg (n=1)	20mg (n=6)	30mg (n=16)	40mg (n=30)	50mg (n=26)	60mg (n=27)	70mg (n=23)
C <sub>avg</sub> (ng/dL)	Mean	196	464	392	444	483	441	415
	SD		205	164	176	156	163	136
C <sub>max</sub> (ng/dL)	Mean	503	971	775	855	964	766	724
	SD		399	278	417	389	292	313

Figure 2 summarizes the pharmacokinetic profiles of total testosterone in patients completing 90 days of testosterone gel treatment administered as 40 mg of testosterone once-daily for the initial 14 days followed by possible titration according to follow-up testosterone measurements.



**Figure 2 Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 90 (N=129)**

Additionally, there were no clinically significant changes from baseline for sex hormone binding globulin (SHBG) (slight decrease), E2 (slight increase) and ratio of DHT to total testosterone (slight increase) at Day 90.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Testosterone gel is supplied in a 60 g canister with a metered dose pump that delivers 10 mg of testosterone per complete pump actuation. The metered dose pump is capable of dispensing 120 metered pump actuations. One pump actuation dispenses 0.5 g of gel. Testosterone gel is available in a 60 g canister NDC 0603-7831-88.

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP]. Do Not Freeze.

Used testosterone gel canisters should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.

**17 PATIENT COUNSELING INFORMATION**

**See FDA-approved Medication Guide.**

Patients should be informed of the following information:

**17.1 Use in Men with Known or Suspected Prostate or Breast Cancer**

Men with known or suspected prostate or breast cancer should not use testosterone gel [see *Contraindications (4) and Warnings and Precautions (5.1)*].

**17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure**

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel in men. Cases of secondary exposure to testosterone in children have been reported.

Physicians should advise patients of the reported signs and symptoms of secondary exposure which may include the following:

- In children; unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.
- In women; changes in hair distribution, increase in acne, or other signs of testosterone effects.
- The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider.
- Testosterone gel should be promptly discontinued until the cause of virilization is identified.

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from testosterone gel in men [see *Medication Guide*]:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using testosterone gel.
- Patients using testosterone gel should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water after application.
  - **Cover the application site(s)** with clothing after the gel has dried.
  - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
- In the event that unwashed or unclothed skin to which testosterone gel has been applied comes in contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible [see *Dosage and Administration (2.2), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)*].

**17.3 Potential Adverse Reactions with Androgens**

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

**17.4 Patients Should Be Advised of the Following Instructions for Use**

- **Read the Medication Guide before starting testosterone gel therapy and reread it each time the prescription is renewed.**
- **Testosterone gel should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women.**
- **Keep testosterone gel out of the reach of children.**
- **Testosterone gel is an alcohol based product and is flammable; therefore avoid fire, flame or smoking until the gel has dried.**
- It is important to adhere to all recommended monitoring.
- Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.
- Testosterone gel is prescribed to meet the patient's specific needs, therefore, the patient should never share testosterone gel with anyone.
- Wait 2 hours before swimming or washing following application of testosterone gel. This will ensure that the greatest amount of testosterone gel is absorbed into their system.

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