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
See Full Prescribing Information for complete boxed warning.
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,).**

----------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 (1):

- Primary Hypogonadism (Congenital or Acquired)
- Hypogonadotropic Hypogonadism (Congenital or Acquired)

Important limitations of use:

- Safety and efficacy of testosterone gel in males <18 years old have not been established. (1, 8.4)
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure (1, 12.3).

----------DOSAGE AND ADMINISTRATION----------

- Recommended starting dose: 50 mg for adult males, applied topically once daily (2.1).
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply testosterone gel to the genitals (2.1, 12.3).
- Dose adjustment for adult males: If serum testosterone concentration is below the normal range, adjust dose from 50 mg to 75 mg and from 75 mg to 100 mg. If the serum testosterone concentration exceeds the normal range, the daily dose should be decreased from 100 mg to 75 mg, and from 75 mg to 50 mg. If the serum testosterone concentration consistently exceeds the normal range at 50 mg, testosterone gel should be discontinued (2.1).
- Patients should wash hands immediately with soap and water after applying testosterone gel and cover the application site(s) 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)

----------DOSAGE FORMS AND STRENGTHS----------

Testosterone gel for topical use is available as:

- 25 mg of testosterone per packet
- 50 mg of testosterone per packet (3)

----------CONTRAINDICATIONS----------

- Men with carcinoma of the breast or known or suspected prostate cancer (4, 5.1)
- Pregnant or breast-feeding 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)
- Exogenous administration of androgens may lead to azoospermia (5.5)
- Edema with or without congestive heart failure (CHF) may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.7)
- Sleep apnea may occur in those with risk factors (5.9)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.6, 5.10)
- Testosterone gel is flammable until dry (5.13)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 5%) are acne, application site reaction, abnormal lab tests, and prostatic disorders (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872 x6351 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Androgens may decrease blood glucose, and therefore insulin requirement in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended (7.2).
- Use of testosterone with 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 is insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 2/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

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 any 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).**

1 INDICATIONS AND USAGE

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

- Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.

- Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels but have gonadotropins in the normal or low range.

Important limitations of use

- Safety and efficacy of testosterone gel in males < 18 years old have not been established [see *Use in Specific Populations (8.4)*].
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure *[see Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Adjustment

The recommended starting dose of testosterone gel is 50 mg of testosterone applied topically once daily in the morning to the shoulders and upper arms.

The dose can be adjusted between a minimum of 50 mg of testosterone and a maximum of 100 mg of testosterone. To ensure proper dosing, the serum testosterone concentrations should be measured periodically and dose should be adjusted so that serum testosterone concentrations remain in the normal range (298 ng/dL to 1043 ng/dL).

If the serum testosterone concentration is below the normal range, the dose may be increased from 50 mg to 75 mg of testosterone, and from 75 mg to 100 mg of testosterone. If the serum testosterone concentration exceeds the normal range, the daily dose should be decreased from 100 mg to 75 mg of testosterone, and from 75 mg to 50 mg of testosterone. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 50 mg of testosterone, therapy with testosterone gel should be discontinued.

2.2 Administration Instructions

Testosterone gel should be applied to clean, dry, intact skin of the upper arms and shoulders and/or abdomen. Do not apply testosterone gel to any other parts of the body, including the genitals *[see Clinical Pharmacology (12.3)]*. Area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt. Patients should be instructed to use the palm of the hand to apply testosterone gel and spread across the maximum surface area as directed in **Figure 1**.

The prescribed daily dose of testosterone gel should be applied to the right and left upper arms and shoulders and/or abdomen as shown in the shaded areas in **Figure 1**.

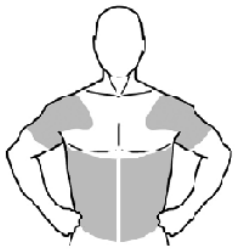


Figure 1: Application Sites for Testosterone gel

Once the application is dry, the site should be covered with clothing *[see Clinical Pharmacology (12.3)]*. Wash hands thoroughly with soap and water. 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 application site for a minimum of 5 hours after application.

To obtain a full dose, the entire packet contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied.

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 upper arms and shoulders and/or abdomen. The area of application should be limited to the area that will be covered by a short sleeve t-shirt.
- Patients should wash their hands with soap and water immediately after applying testosterone gel.
- Patients should cover the application site(s) with clothing (e.g., a t-shirt) after the gel has dried.
- Prior to situations in which direct skin-to-skin contact 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 unit-dose packets:

- 25 mg of testosterone per packet
- 50 mg of testosterone per packet

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) and 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 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 *Warnings and Precautions (5.2)* and *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 patients for 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 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)*].

5.5 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.

5.6 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 intramuscular testosterone enanthate has produced multiple hepatic adenomas. Testosterone gel is not known to cause these adverse effects.

5.7 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)*].

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

5.9 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.

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

5.11 Hypercalcemia
Androgens, including testosterone gel, 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.

5.12 Decreased Thyroxine-binding Globulin

Androgens, including testosterone gel, may decrease concentrations of thyroxin-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.

5.13 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 Trials 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 practice.

Clinical Trials in Hypogonadal Men

Table 1 shows the incidence of all adverse reactions with testosterone gel and reported by > 1% of patients in a 180 Day, Phase 3 study.

Table 1: Adverse Reactions to Testosterone Gel in the 180 Day Controlled Clinical Trial

	Dose of Testosterone		
Adverse Reaction	50 mg	75 mg	100 mg
	N = 77	N = 40	N = 78
Acne	1%	3%	8%
Alopecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder***	3%	0%	0%

**Lab test abnormal* occurred in nine patients with one or more of the following events reported: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine, elevated total bilirubin.
***Prostate disorders* included five patients with enlarged prostate, one with BPH, and one with elevated PSA results.
****Testis disorders* were reported in two patients: one with left varicocele and one with

slight sensitivity of left testis.

Other less common adverse reactions, reported in fewer than 1% of patients included: amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

In this 180 day clinical trial, skin reactions at the site of application were reported with testosterone gel, but none was severe enough to require treatment or discontinuation of drug.

Six patients (4%) in this trial had adverse events that led to discontinuation of testosterone gel. These events included: cerebral hemorrhage, convulsion, depression, sadness, memory loss, elevated prostate specific antigen, and hypertension. No testosterone gel patient discontinued due to skin reactions.

In a separate uncontrolled pharmacokinetic study of 10 patients, two had adverse reactions; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other.

In a 3 year, flexible dose, extension study, the incidence of all adverse reactions to testosterone gel and reported by > 1% of patients is shown in **Table 2**.

Table 2: Adverse Reactions to Testosterone gel in the 3 Year, Flexible Dose, Extension Study

Adverse Reaction	Percent of Subjects
	(N = 162)
Lab Test Abnormal+	9.3
Skin dry	1.9
Application Site Reaction	5.6
Acne	3.1
Pruritus	1.9
Enlarged Prostate	11.7
Carcinoma of Prostate	1.2
Urinary Symptoms*	3.7
Testis Disorder**	1.9
Gynecomastia	2.5
Anemia	2.5

+*Lab test abnormal* occurred in 15 patients with one or more of the following events reported: elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, elevated HDL, elevated serum creatinine.
**Urinary symptoms* included nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream.
***Testis disorders* included three patients. There were two with a non-palpable testis and one with slight right testicular tenderness.

Two patients reported serious adverse events: deep vein thrombosis (DVT) and prostate disorder requiring a transurethral resection of the prostate (TURP).

Discontinuation for adverse events in this study included: two patients with application site reactions, one with kidney failure, and five with prostate disorders (including increase in serum PSA in 4 patients, and increase in PSA with prostate enlargement in a fifth patient).

Increases in Serum PSA Observed in Clinical Trials of Hypogonadal Men
During the initial 6-month study, the mean change in PSA values had a statistically significant increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter in the 162 hypogonadal men on testosterone gel in the 3 year extension study. There was no additional statistically significant increase observed in mean PSA from 6 months through 36 months. However, there were increases in serum PSA observed in approximately 18% of individual patients. The overall mean change from baseline in serum PSA values for the entire group from month 6 to 36 was 0.11 ng/mL.

Twenty-nine patients (18%) met the per-protocol criterion for increase in serum PSA, defined as > 2X the baseline or any single serum PSA > 6 ng/mL. Most of these (25/29) met this criterion by at least doubling of their PSA from baseline. In most cases where PSA at least doubled (22/25), the maximum serum PSA value was still < 2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%).

Four patients met this criterion by having a serum PSA > 6 ng/mL and in these, maximum serum PSA values were 6.2 ng/mL, 6.6 ng/mL, 6.7 ng/mL, and 10.7 ng/mL. In two of these patients, prostate cancer was detected on biopsy. The first patient's PSA levels were 4.7 ng/mL and 6.2 ng/mL at baseline and at Month 6/Final, respectively. The second patient's PSA levels were 4.2 ng/mL, 5.2 ng/mL, 5.8 ng/mL, and 6.6 ng/mL at baseline, Month 6, Month 12, and Final, respectively.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of testosterone gel. 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.

Secondary Exposure to Testosterone in Children

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarket surveillance. 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)*].

Hypogonadal Men
Table 3 includes adverse reactions that have been identified postmarketing.

Table 3: Adverse Reactions from Postmarketing Experience of Testosterone Gel by MedDRA System Organ Class

Blood and the lymphatic system disorders:	Elevated Hgb, Hct (polycythemia)
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders and administration site reactions:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination
Hepatobiliary disorders:	Abnormal liver function tests (e.g., transaminases, elevated GGTP, bilirubin)

Investigations:	Elevated PSA, electrolyte changes (nitrogen, calcium, potassium, phosphorus, sodium), changes in serum lipids (hyperlipidemia, elevated triglycerides, decreased HDL), impaired glucose tolerance, fluctuating testosterone levels, weight increase
Neoplasms benign, malignant and unspecified (cysts and polyps):	Prostate cancer
Nervous system:	Headache, dizziness, sleep apnea, insomnia
Psychiatric disorders:	Depression, emotional lability, decreased libido, nervousness, hostility, amnesia, anxiety
Reproductive system and breast disorders:	Gynecomastia, mastodynia, prostatic enlargement, testicular atrophy, oligospermia, priapism (frequent or prolonged erections)
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (pruritus, dry skin, erythema, rash, discolored hair, paresthesia), sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes)

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, insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

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 apprised of the potential hazard to a 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
Safety and effectiveness of testosterone gel in males < 18 years old have 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. Additionally, there is insufficient long-term safety data in geriatric patients to assess the potentially increased risk 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 formal studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment
No formal studies were conducted involving patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
Testosterone gel contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

9.2 Abuse
Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence
Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drugs are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of a withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

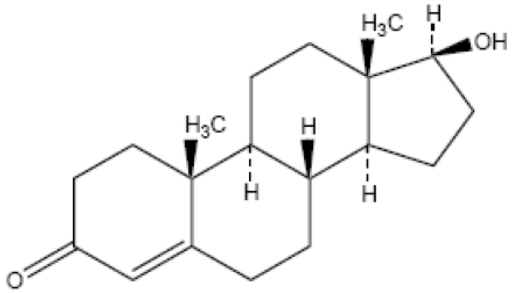
There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.

Treatment of overdosage would consist of discontinuation of testosterone gel together with appropriate symptomatic and supportive care.

11 DESCRIPTION

Testosterone gel is a clear, colorless hydroalcoholic gel containing testosterone. Topical administration of testosterone gel is to be applied daily to the skin’s surface. Testosterone gel is supplied as 25 mg of testosterone in 2.5 g of gel and 50 mg of testosterone in 5 g of gel.

The active pharmacologic ingredient in testosterone gel is testosterone. Testosterone USP is a white to slightly creamy white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



Testosterone

$C_{19}H_{28}O_2$ M.W. 288.42

Inactive ingredients in testosterone gel are carbomer homopolymer type C, dehydrated alcohol 67%, isopropyl palmitate, purified water, and sodium hydroxide.

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 maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism 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

In a single-dose, two-way crossover clinical study conducted in 72 hypogonadal males under fasting conditions, the testosterone exposure ($AUC_{0\text{-}60}$) and maximum testosterone concentration (C_{max}) following a topical administration of 100 mg testosterone administered as 2 x 5 g testosterone gel packets (1 packet applied on each shoulder/upper arm) on a designated area of 500 cm^2 were comparable to those following a topical administration of an approved testosterone gel product.

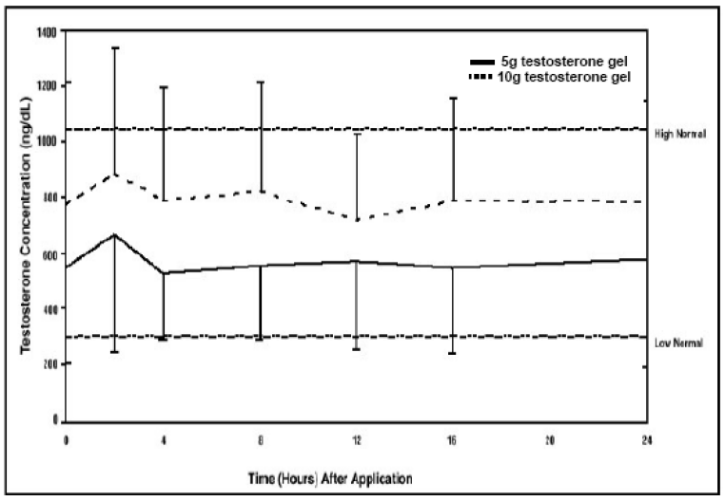
Testosterone gel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (298 to 1043 ng/dL) seen in healthy men.

Testosterone gel provides continuous transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

Testosterone gel is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from testosterone gel is absorbed into systemic circulation. Therefore, 5 g and 10 g of testosterone gel systemically deliver approximately 5 mg and 10 mg of testosterone, respectively. In a study with 10 g of testosterone gel, all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24 hour dosing interval. Serum concentrations approximate the steady-state concentration by the end of the first 24 hours and are at steady state by the second or third day of dosing.

With single daily applications of testosterone gel, follow-up measurements 30, 90, and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. **Figure 2** summarizes the 24-hour pharmacokinetic profiles of testosterone for hypogonadal men (< 300 ng/dL) maintained on 5 g or 10 g of testosterone gel for 30 days. The average (± SD) daily testosterone concentration produced by 10 g on Day 30 was 792 (± 294) ng/dL and by testosterone gel 5 g was 566 (± 262) ng/dL.

Figure 2: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying Testosterone Gel Once Daily



When testosterone gel treatment is discontinued after achieving steady state, serum testosterone concentrations remain in the normal range for 24 to 48 hours but return to their pretreatment levels by the fifth day after the last application.

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 bound to albumin and other proteins.

Metabolism

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

DHT concentrations increased in parallel with testosterone concentrations during testosterone gel treatment. After 180 days of treatment in adult males, mean DHT concentrations were within the normal range with 5 g testosterone gel and were about 7% above the normal range after a 10 g dose. The mean steady-state DHT/T ratio during 180 days of testosterone gel treatment remained within normal limits and ranged from 0.23 to 0.29 (5 g/day) and from 0.27 to 0.33 (10 g/day).

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.

Potential for testosterone transfer

The potential for testosterone transfer following testosterone gel use was evaluated in a clinical study between males dosed with testosterone gel and their untreated female partners. Two (2) hours after application of 100 mg of testosterone from 10 g of testosterone gel to upper arm and shoulder of one side by the male subjects, the couples (N = 48 couples) engaged in a 15 minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the testosterone gel application sites. Serum concentrations of testosterone were monitored in the female subjects for 24 hours after the transfer procedure. Under these study conditions, all unprotected female partners had a serum testosterone concentration > 2 times the baseline value derived from a 24 hour testosterone concentration measurement during the study. When a shirt covered the application site, study results show an 11% and 16% increase in testosterone $AUC_{0\text{-}24}$ and testosterone C_{max}, respectively, compared to baseline in these females. The potential for dermal testosterone transfer following testosterone gel application on the abdomen has not been evaluated.

In a separate clinical study conducted to evaluate the effect of hand washing on the residual amount of testosterone, 39 healthy male subjects received 100 mg of testosterone from 10 g (2 x 5 g packets) of testosterone gel on the upper arm and shoulder of one side. Subjects washed their hands with liquid soap and warm tap water 5 minutes after drug application. Then hands were wiped with 3 ethanol dampened gauzes per hand which were then combined together and analyzed for testosterone content. A mean (SD) of 284.9 (131) mcg of residual testosterone (i.e., approximately 0.29% of the theoretical dose of 100 mg testosterone administered) was recovered after washing hands with liquid soap and warm tap water.

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, the implant induced cervical-uterine tumors, 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. 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 Trials in Adult Hypogonadal Males

Testosterone gel was evaluated in a multi-center, randomized, parallel-group, active-controlled, 180 day trial in 227 hypogonadal men. The study was conducted in 2 phases. During the Initial Treatment Period (Days 1 to 90), 73 patients were randomized to testosterone gel 5 g daily, 78 patients to testosterone gel 10 g daily, and 76 patients to a non-scrotal testosterone transdermal system. The study was double-blind for dose of testosterone gel but open-label for active control. Patients who were originally randomized to testosterone gel and who had single-sample serum testosterone levels above or below the normal range on Day 60 were titrated to 7.5 g daily on Day 91. During the Extended Treatment Period (Days 91 to 180), 51 patients continued on testosterone gel 5 g daily, 52 patients continued on testosterone gel 10 g daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received testosterone gel 7.5 g daily. Upon completion of the initial study, 163 enrolled and 162 patients received treatment in an open-label extension study of testosterone gel for an additional period of up to 3 years.

Mean peak, trough and average serum testosterone concentrations within the normal range (298 to 1043 ng/dL) were achieved on the first day of treatment with doses of 5 g and 10 g. In patients continuing on testosterone gel 5 g and 10 g, these mean testosterone levels were maintained within the normal range for the 180-day duration of the original study. **Figure 3** summarizes the 24 hour pharmacokinetic profiles of testosterone administered as testosterone gel for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed testosterone gel treatment.

Figure 3: Mean Steady State Testosterone Concentrations in Patients with Once-Daily Testosterone Gel Therapy

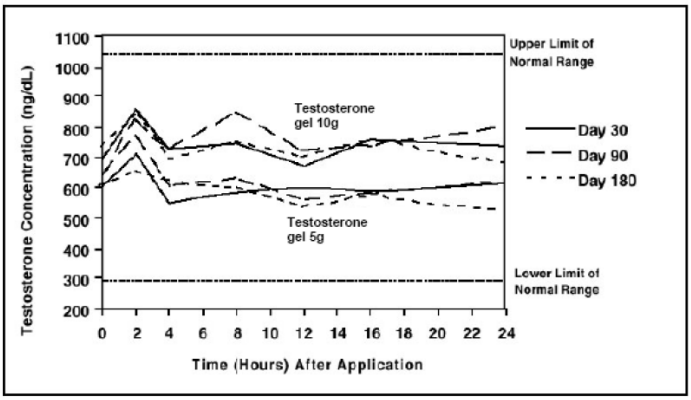


Table 4 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 5 g, 7.5 g, or 10 g of testosterone gel. The 7.5 g dose produced mean concentrations intermediate to those produced by 5 g and 10 g of testosterone gel.

Table 4: Mean (± SD) Steady-State Serum Testosterone Concentrations During Therapy (Day 180)

	5 g N = 44	**7.5 g** N = 37	**10 g** N = 48
C_{avg}	555 ± 225	601 ± 309	713 ± 209
C_{max}	830 ± 347	901 ± 471	1083 ± 434
C_{min}	371 ± 165	406 ± 220	485 ± 156

Of 129 hypogonadal men who were appropriately titrated with testosterone gel and who had sufficient data for analysis, 87% achieved an average serum testosterone level within the normal range on Treatment Day 180.

In patients treated with testosterone gel, there were no observed differences in the average daily serum testosterone concentrations at steady-state based on age, cause of hypogonadism, or body mass index.

DHT concentrations increased in parallel with testosterone concentrations at testosterone gel doses of 5 g/day and 10 g/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with testosterone gel 5 or 10 g/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of SHBG decreased very slightly (1 to 11%) during testosterone gel treatment. In men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and time-dependent manner during treatment with testosterone gel.

16 HOW SUPPLIED/STORAGE AND HANDLING

Testosterone gel is supplied in unit-dose foil packets in cartons of 30.

- 25 mg of testosterone per packet. Each packet contains 2.5 g of gel. NDC 0093-5865-55
- 50 mg of testosterone per packet. Each packet contains 5 g of gel. NDC 0093-5866-55

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

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.

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 have been reported in children with signs and symptoms including enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.

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.

- **To minimize the potential for transfer** to others, 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.

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 to 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.**

- **Testosterone gel should be used only in the prescribed doses and application instructions.**

- 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 5 hours before showering or swimming. This will ensure that the greatest amount of testosterone gel is absorbed into their system.

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