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, 17).**

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	5/2015
Dosage and Administration (2)	5/2015
Warnings and Precautions (5.5)	5/2015
Warnings and Precautions (5.4)	6/2014

----------INDICATIONS AND USAGE----------
Testosterone 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 less than 18 years old have not been established. (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----------
- 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 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet), applied once daily in the morning. (2.1).
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply testosterone gel to any other parts of the body including the genitals, chest, armpits (axillae), knees, or back. (2.2).
- Dose adjustment: Testosterone gel can be dose adjusted using 50 mg, 75 mg, or 100 mg of testosterone on the basis of total serum testosterone concentration.. Additionally, serum testosterone concentration should be assessed periodically. (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 follows:
- Metered-dose pump that delivers 12.5 mg of testosterone per actuation. (3)
- Packets containing 25 mg of testosterone. (3)
- Packets containing 50 mg of testosterone. (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/neonatal 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 (5.7).
- Edema, with or without congestive heart failure (CHF), may be a complication in patients with preexisting cardiac, renal, or hepatic diseases (5.9, 6.2).
- Sleep apnea may occur in those with risk factors (5.11).
- Monitor serum testosterone, prostatic specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.8, 5.12).
- Testosterone gel is flammable until dry (5.15).

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

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or *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 Medication Guide

Revised: 05/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

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 any unwashed or unclothed application sites in men using testosterone gel [*see Dosage and Administration (2.2), 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)*].**

1 INDICATIONS AND USAGE

Testosterone gel is 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 conditions such as 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 concentrations and gonadotropins (follicle stimulating hormone (FSH), lutenizing 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 testosterone serum 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 less than 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. (1, 12.3)

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 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet), applied topically once daily in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day).

Dose Adjustment

To ensure proper dosing, serum testosterone levels should be measured at intervals. If the serum testosterone concentration is below the normal range, the daily testosterone gel dose may be increased from 50 mg to 75 mg and from 75 mg to 100 mg for adult males as instructed by the physician (see Table 1, Dosing Information for testosterone gel). If the serum testosterone concentration exceeds the normal range, the daily testosterone gel dose may be decreased. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 50 mg, testosterone gel therapy should be discontinued. In addition, serum testosterone concentration should be assessed periodically.

2.2 Administration Instructions

Testosterone gel should be applied to clean, dry, healthy, intact skin of the right and left upper arms/ shoulders and/or right and left abdomen. Area of application should be limited to the area that will be covered by the patient's short sleeve T- shirt. Do not apply testosterone gel to any other part of the body including the genitals, chest, armpits (axillae), knees, or back. Testosterone *g*el should be evenly distributed between the right and left upper arms/shoulders or both sides of the abdomen.

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

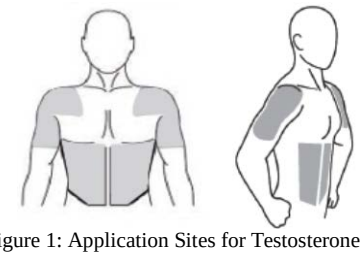


Figure 1: Application Sites for Testosterone gel

After applying the gel, the application site should be allowed to dry prior to dressing. Hands should be washed with soap and water after testosterone gel has been applied. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including testosterone gel, are flammable.

The patient should be advised to avoid swimming or showering for at least 5 hours after the application of testosterone gel.

Multi-Dose Pump

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 three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose. After the priming procedure, patients should completely depress the pump one time (actuation) for every 12.5 mg of testosterone required to achieve the daily prescribed dosage. The product should be delivered directly into the palm of the hand and then applied to the desired application sites. Alternatively, testosterone gel can be applied directly to the application sites. Table 1 provides dosing information for adult males.

Table 1: Dosing Guidelines for Using the Multi-Dose Pump

Prescribed Daily Dose	Number of Pump Actuations
50 mg	4 (once daily)
75 mg	6 (once daily)
100 mg	8 (once daily)

Packets

The entire 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.
- 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., a T-shirt) 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 is available as follows:

- A metered-dose pump. Each pump actuation delivers 12.5 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel.
- A unit dose packet containing 50 mg of testosterone provided in 5 g of gel.

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), and Nonclinical Toxicology (13.1)]*.

- 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 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 for 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. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens [*see Contraindications (4), Adverse reactions (6.1) and Nonclinical Toxicology (13.1)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. 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 testosterone gel. 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 [see Adverse Reactions (6.2)].

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 Use in Women

Due to 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)]*.

5.7 Potential for Adverse Effects on Spermatogenesis

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

5.8 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 produce these adverse effects.

5.9 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 preexisting cardiac, renal, or hepatic disease *[see Adverse Reactions (6.2)]*.

5.10 Gynecomastia

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

5.11 Sleep Apnea

The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases *[see Adverse Reactions (6.2)]*.

5.12 Lipids

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

5.13 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.

5.14 Decreased Thyroxine-binding Globulin

Androgens, including testosterone gel, may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.15 Flammability

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

Clinical Trials in Hypogonadal Men

Table 2 shows the incidence of all adverse reactions with testosterone gel and reported by > 1% of patients in a 180 Day, Phase 3 study.

Table 2: 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%

Abnormal Lab Tests *	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%

**Abnormal lab tests* 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 reactions that led to discontinuation of testosterone gel. These reactions included: cerebral hemorrhage, convulsion, depression, sadness, memory loss, elevated prostate specific antigen, and hypertension. No patients on testosterone gel 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 3**:

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

Adverse Reaction	Percent of Subjects
	(N = 162)
Abnormal Lab Tests+	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

+*Abnormal lab tests* 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 reactions considered possibly related to treatment: deep vein thrombosis (DVT) and prostate disorder requiring a transurethral resection of the prostate (TURP).

Discontinuation for adverse reactions 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 (Table 4):

Table 4: Adverse Reactions from Postmarketing Experience of Testosterone Gel by MedDRA System Organ Class

Blood and the lymphatic system disorders:	Elevated Hgb, Hct (polycythemia)
Cardiovascular disorders:	Myocardial infarction, stroke
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), venous thromboembolism

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)]*.

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 use 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, such as testosterone, 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 efficacy of testosterone gel in pediatric males less than 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. Additionally, there is 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 involving 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

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

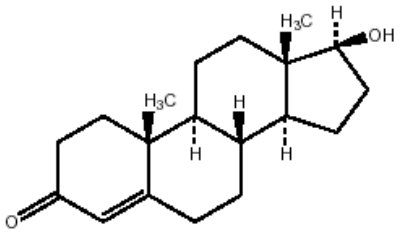
There is one report of acute overdosage with use of an approved injectable testosterone product: This subject had serum testosterone concentrations of up to 11, 400 ng/dL with a cerebrovascular accident.

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 hydroalcoholic gel containing testosterone.

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



Testosterone
$C_{19}H_{28}O_2$ MW 288.42

Inactive ingredients in testosterone gel are carbomer 980, ethanol 67.0%, isostearic acid, purified water, and sodium hydroxide. These ingredients are not pharmacologically active.

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, a clinical syndrome resulting from insufficient secretion of testosterone, can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, while 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, crossover clinical study conducted in 24 hypogonadal males under fasting conditions, the serum testosterone exposure (AUC_{0-72}) and maximum testosterone concentration (C_{max}) following a topical administration of 100 mg testosterone administered as 2 x 5 g testosterone gel packets (2 packets applied to the shoulder/upper arm) were bioequivalent to those following a topical administration of an approved testosterone gel product.

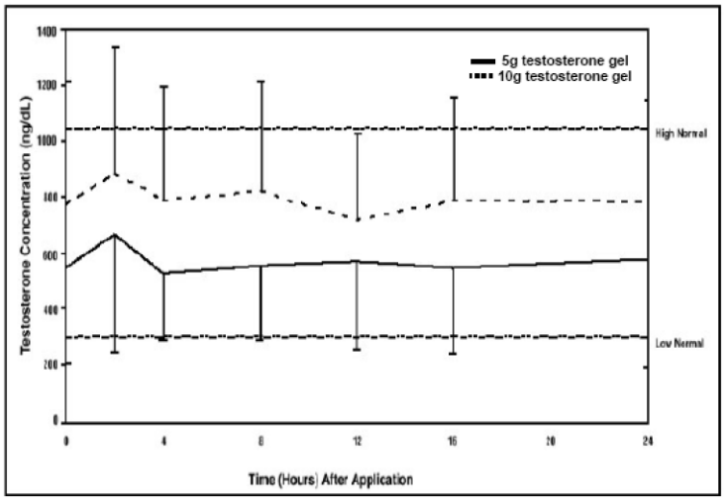
Testosterone gel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (298 to 1043 ng/dL) seen in healthy men.

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. In a study with testosterone gel 100 mg, 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 testosterone gel 50 mg or 100 mg of for 30 days. The average (± SD) daily testosterone concentration produced by 100 mg on Day 30 was 792 (± 294) ng/dL and by testosterone gel 50 mg was 566 (± 262) ng/dL.

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



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

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. 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

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 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.

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 concentrations by the fifth day after the last application.

Testosterone Transfer from Male Patients to Female Partners

The potential for dermal 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 (2 x 5 g packets) of testosterone gel to upper arm and shoulder of one side by the male subjects, the couples (N = 20 couples) engaged in

a 15 minute session 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, unprotected female partners had a mean testosterone AUC_{0-24} and C_{max} that were more than 2 times greater than their mean baseline values. When a shirt covered the application site, study results showed a 16% and 48% increase in testosterone AUC_{0-24} and 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.

Effect of Hand Washing and Showering

In a separate clinical study conducted to evaluate the effect of hand washing on the residual amount of testosterone, 33 healthy male subjects received 100 mg of testosterone from 10 g (2 x 5 g packets) of testosterone gel on a hand and applied testosterone gel to the upper arm and shoulder of one side. Subjects washed their hands with liquid soap and warm tap water immediately after drug application. Then the hand was wiped with 3 ethanol dampened gauzes which were then combined together and analyzed for testosterone content. A mean (SD) of 0.40 (0.20) mg of residual testosterone (i.e., approximately 0.4% of the theoretical dose of 100 mg testosterone administered) was recovered after washing hands with liquid soap and warm tap water.

The same study also evaluated the effect of showering on the residual amount of testosterone on the application site. Subjects washed the application site by showering two hours after drug application. The application site was then wiped with 3 ethanol dampened gauzes which were then combined together and analyzed for testosterone content. A mean (SD) of 5.80 (2.77) mg of residual testosterone (i.e., approximately 5.8% of the theoretical dose of 100 mg testosterone administered) was recovered after showering.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

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.

Mutagenesis

Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays.

Impairment of Fertility

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 50 mg daily, 78 patients to testosterone gel 100 mg 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 75 mg daily on Day 91. During the Extended Treatment Period (Days 91 to 180), 51 patients continued on testosterone gel 50 mg daily, 52 patients continued on testosterone gel 100 mg daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received testosterone gel 75 mg 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 50 mg and 100 mg of testosterone gel. In patients continuing on testosterone gel 50 mg and 100 mg, 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

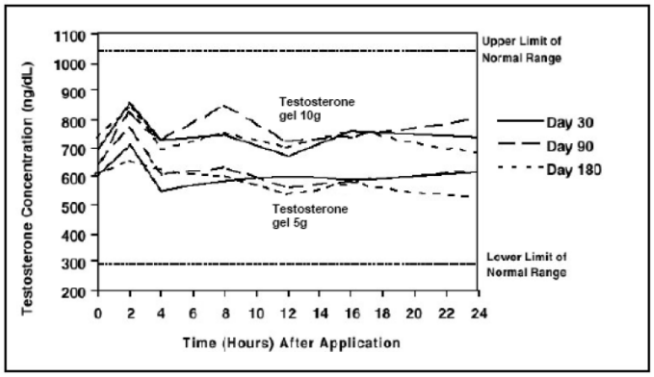


Table 5 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 50 mg, 75 mg, or 100 mg, of testosterone. The 75 mg dose produced mean concentrations intermediate to those produced by 50 mg and 100 mg of testosterone.

Table 5: Mean (± SD) Steady-State Serum Testosterone Concentrations During Therapy (Day 180)

	50 mg N = 44	**75 mg** N = 37	**100 mg** 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.

14.2 Skin Irritation Study

Testosterone gel was evaluated in a randomized, five-treatment, single-center, controlled, within-subject comparison study with healthy subjects using a cumulative irritation patch test design. Thirty-three (33) subjects completed the study involving testosterone gel, a comparator control product, vehicle, and positive and negative controls. All five treatments were applied to the skin separately with an occlusive patch. Each subject received a set of 5 patches, once daily for 21 consecutive days. Evaluation of dermal reactions at the application sites were assessed every day at the time of removal of each patch using an established ordinal (6-point) scoring system. Testosterone gel showed no evidence of significant irritation and was statistically significantly less irritating than the positive control ($P<0.001$).

14.3 Skin Sensitization Study

Testosterone gel was evaluated in a randomized, five-treatment, single-center, controlled, within-subject study to evaluate the sensitizing potential on healthy volunteers, using a Repeat Insult Patch Test design. Two hundred three (203) subjects completed the study involving Testosterone Gel, a comparator control product, vehicle, and positive and negative controls. All five treatments were applied to the skin separately with an occlusive patch. Each subject received a set of 5 patches, every 48-72 hours for 21 consecutive days. Evaluation of dermal reactions at the application sites were assessed clinically every day at the time of removal of each patch using an established ordinal (6-point) scoring system. Observations at the naïve site during challenge and the pattern of reactivity during induction provided bases for an interpretation of contact sensitizations. Under these conditions there was no evidence of sensitization to testosterone gel, In the cumulative irritancy analysis, testosterone gel was statistically significantly less irritating than the positive control ($P<0.001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Testosterone gel is supplied in non-aerosol, metered-dose pumps that deliver 12.5 mg of testosterone per complete pump actuation. The pumps are composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88 g metered-dose Pump is capable of dispensing 75 g of gel or 60 metered pump actuations; each pump actuation dispenses 1.25 g of gel containing 12.5 mg of testosterone.

NDC Number	Package Size
45802-116-02	2 x 75 g pumps (each pump dispenses 60 metered pump actuations with each pump actuation containing 12.5 mg of testosterone in 1.25 g of gel)

Testosterone gel is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

NDC Number	Package Size
45802-116-65	30 packets (25 mg of testosterone in 2.5 g of gel per packet)
45802-116-39	30 packets (50 mg of testosterone in 5 g of gel per packet)

16.2 Storage and Handling

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

16.3 Disposal

Used testosterone gel pumps or used testosterone gel packets 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 patient labeling (Medication Guide)

Patients should be informed of the following:

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 have been reported in children.

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.

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

Made in Israel
Manufactured by Perrigo-Israel Pharmaceuticals Ltd., Yeruham 80500, Israel
Distributed by Perrigo, Allegan, MI 49010

Rev: 05/2015

1C200 RC J4

MEDICATION GUIDE

testosterone gel
Testosterone (tes-TOS-te-rone gel) CIII

Read this Medication Guide that comes with testosterone gel before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about testosterone gel?

1. **Early signs and symptoms of puberty have happened in young children who were accidentally exposed to testosterone through contact with men using testosterone gel.**

   Signs and symptoms of early puberty in a child may include:

   - enlarged penis or clitoris
   - early development of pubic hair
   - increased erections or sex drive
   - aggressive behavior

   Testosterone gel can transfer from your body to others.

2. **Women and children should avoid contact with the unwashed or unclothed area where testosterone gel has been applied to your skin.**

   Stop using testosterone gel and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to testosterone gel.

   Signs and symptoms of exposure to testosterone gel in children may include:

   - enlarged penis or clitoris
   - early development of pubic hair
   - increased erections or sex drive
   - aggressive behavior

   Signs and symptoms of exposure to testosterone gel in women may include:

   - changes in body hair
   - a large increase in acne

   To lower the risk of transfer of testosterone gel from your body to others, you should follow these important instructions:

- **Apply testosterone gel only to areas that will be covered by a short sleeve T-shirt.** These areas are your shoulders and upper arms, or stomach area (abdomen), or shoulders, upper arms and stomach area.
- **Wash your hands right away** with soap and water after applying testosterone gel.
- **After the gel has dried, cover the application area with clothing.** Keep the area covered until you have washed the application area well or have showered.
- **If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.**
- **If a woman or child makes contact with the testosterone gel application area, that area on the woman or child should be washed well with soap and water right away.**

What is testosterone gel?

Testosterone gel is a prescription medicine that contains testosterone. Testosterone gel is used to treat adult males who have low or no testosterone due to certain medical conditions.

Your healthcare provider will test your blood before you start and while you are using testosterone gel.

It is not known if testosterone gel is safe or effective to treat men who have low testosterone due to aging.

It is not known if testosterone gel is safe or effective in children younger than 18 years old. Improper use of testosterone gel may affect bone growth in children.

Testosterone gel is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your testosterone gel in a safe place to protect it. Never give your testosterone gel to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

Testosterone gel is not meant for use in women.

Who should not use testosterone gel?

Do not use testosterone gel if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or breast-feeding. Testosterone gel may harm your unborn or breast-feeding baby.

Women who are pregnant or who may become pregnant should avoid contact with the area of skin where testosterone gel has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using testosterone gel?

Before you use testosterone gel, tell your healthcare provider if you:

- have breast cancer
- Have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have liver or kidney problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using testosterone gel with certain other medicines can affect each other.

Especially, tell your healthcare provider if you take:

- insulin
- corticosteroids
- medicines that decrease blood clotting

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use testosterone gel?

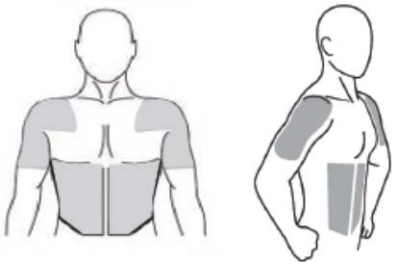
- It is important that you apply testosterone gel exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much testosterone gel to apply and when to apply it.
- Your healthcare provider may change your testosterone gel dose. **Do not** change your testosterone gel dose without talking to your healthcare provider.
- **Testosterone gel is to be applied to the area of your shoulders, upper arms, or abdomen that will be covered by a short sleeve t-shirt. Do not** apply testosterone gel to any other parts of your body such as your penis, scrotum, chest, armpits (axillae), knees, or back.

- Apply testosterone gel at the same time each morning. Testosterone gel should be applied after showering or bathing.
- **Wash your hands right away** with soap and water after applying testosterone gel.
- Avoid showering, swimming, or bathing for at least 5 hours after you apply testosterone gel.
- Testosterone gel is flammable until dry. Let testosterone gel dry before smoking or going near an open flame.
- Let the application areas dry before putting on a t-shirt.

Applying testosterone gel:

Testosterone gel comes in a pump or in packets.

- **Before applying testosterone gel, make sure that your shoulders, upper arms, and abdomen are clean, dry, and there is no broken skin.**
- The application sites for testosterone gel are the shoulders, upper arms, or abdomen that will be covered by a short sleeve t-shirt (See Figure A).



(Figure A)

If you are using the testosterone gel pump:

- Before using a new bottle of testosterone gel for the first time, you will need to prime the pump. To prime the testosterone gel pump, slowly push the pump all the way down 3 times.
- **Do not** use any testosterone gel that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your testosterone gel pump is now ready to use.
- Remove the cap from the pump. Then, position the nozzle over the palm of your hand and slowly push the pump all the way down. Apply testosterone gel to the application site. You may also apply testosterone gel directly to the application site.
- **Wash your hands with soap and water right away.**
- Your healthcare provider will tell you the number of times to press the pump for each dose.

If you are using testosterone gel packets:

- Tear open the packet completely at the dotted line. Squeeze from the bottom of the packet to the top.
- Squeeze all of the testosterone gel out of the packet into the palm of your hand. Apply testosterone gel to the application site. You may also apply testosterone gel from the packet directly to the application site.
- Testosterone gel should be applied right away.
- **Wash your hands with soap and water right away.**

What are the possible side effects of testosterone gel?

Testosterone gel can cause serious side effects including:

- See "What is the most important information I should know about testosterone gel?"
- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using testosterone gel.** This can include:
  - increased urination at night
  - trouble starting your urine stream
  - having to pass 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 or weak urine flow
- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use testosterone gel.
- Blood clots in the legs or lungs. Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- Possible increased risk of heart attack or stroke.
- **In large doses testosterone gel may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Have problems breathing while you sleep (sleep apnea).**

Call your healthcare provider right away if you have any of the serious side effects listed above.
The most common side effects of testosterone gel include:

- acne

- skin irritation where testosterone gel is applied
- lab test changes
- increased prostate specific antigen (a test used to screen for prostate cancer)

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of testosterone gel. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store testosterone gel?

- Store testosterone gel between 68ºF to 77ºF (20ºC to 25ºC).
- Safely throw away used testosterone gel in household trash. Be careful to prevent accidental exposure of children or pets.
- Keep testosterone gel away from fire.

Keep testosterone gel and all medicines out of the reach of children.

General information about the safe and effective use of testosterone gel.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use testosterone gel for a condition for which it was not prescribed. Do not give testosterone gel to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about testosterone gel. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about testosterone gel that is written for health professionals.

For more information, go to www.perrigo.com or call 1-866-634-9120

What are the ingredients in testosterone gel?

Active ingredient: testosterone

Inactive ingredients: carbomer 980, ethyl alcohol 67.0%, isostearic acid, purified water and sodium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Made in Israel

Manufactured by Perrigo,

Yeruham 80500, Israel

Distributed By

[graphic] PERRIGO®

Allegan, MI 49010

www.perrigo.com

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Initial REMS Approval: 1/2013

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NDA 203098 Testosterone Gel, CIII

Drug Class and Formulation: Testosterone Gel Products

Perrigo Israel Pharmaceuticals Ltd.

Industrial Zone

Yeruham, Israel 80500

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(s):

To inform patients about the serious risks associated with the use of testosterone gel.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each testosterone gel, prescription in accordance with 21 CFR § 208.24.

The Medication Guide is appended.

B. Timetable for Submission of Assessments

Perrigo Israel Pharmaceuticals Ltd. will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Perrigo Israel Pharmaceuticals Ltd. will submit each assessment so that it will be received by FDA on or before the due date.