HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOGELXO safely and effectively. See full prescribing information for VOGELXO.

VOGELXO™ (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)**

----------INDICATIONS AND USAGE----------
Vogelxo is an androgen indicated for testosterone 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 Vogelxo 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----------
- Recommended starting dose for adult males: 50 mg of testosterone (one tube or one packet or 4 pump actuations) applied topically once daily at approximately the same time each day. (2.1)
- Apply to clean, dry, intact skin of the shoulders and/or upper arms. Do not apply Vogelxo to the genitals or abdomen. (2.1, 2.2)
- If morning pre-dose serum testosterone concentration is below the normal range, increase dose to 100 mg. (2.1)
- Pre-dose serum testosterone concentration should be assessed periodically. (2.1)
- Patients should wash hands with soap and water immediately after applying Vogelxo and cover application site(s) with clothing after gel has dried. Wash the application sites 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----------
Topical Gel available as:
- 50 mg of testosterone in a unit-dose tube. (3)
- 50 mg of testosterone in a unit-dose packet. (3)
- 12.5 mg of testosterone per one pump actuation in a metered-dose pump. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to Vogelxo. Secondary exposure to testosterone can produce signs of virilization. Vogelxo 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)
- Exogenous administration of androgens may lead to azoospermia. (5.6)
- Edema, with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.8, 6.2)
- Sleep apnea may occur in those with risk factors. (5.10)
- Monitor prostate specific antigen (PSA), hematocrit, and lipid concentrations periodically. (5.1, 5.3, 5.11)
- Vogelxo is flammable until dry. (5.14)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (incidence ≥ 2% of the testosterone gel patients and greater than placebo) are application site reactions and increased hematocrit. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UPSHER-SMITH LABORATORIES, INC. at 1-855-899-9180 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 in patients taking warfarin. (7.2)
- Use of testosterone with 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----------
Geriatric Patients: There are insufficient long-term safety data to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 6/2014

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

1 INDICATIONS AND USAGE

Vogelxo is indicated for testosterone 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 (follicle-stimulating hormone [FSH], luteinizing hormone [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.

Limitations of use:

- Safety and efficacy of Vogelxo 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 *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Adjustment

The recommended starting dose of Vogelxo is 50 mg of testosterone (one tube, one packet, or 4 pump actuations) applied topically once daily at approximately the same time each day to clean, dry intact skin of the shoulders and/or upper arms.

Dose Adjustment

To ensure proper dosing, serum testosterone concentrations should be measured. Morning, pre-dose serum testosterone concentrations should be measured approximately 14 days after initiation of therapy to ensure proper serum testosterone concentrations are achieved. If the serum testosterone concentration is below the normal range (300 ng/dL to 1,000 ng/dL), the daily Vogelxo dose may be increased from 50 mg testosterone (one tube, one packet, or 4 pump actuations) to 100 mg of testosterone (two tubes, two packets, or 8 pump actuations) once daily.

The maximum recommended dose of Vogelxo is 100 mg once daily.

2.2 Administration Instructions

Unit-Dose Tube or Packet

Upon opening the tube or packet the entire contents should be squeezed into the palm of the hand and immediately applied to the shoulders and/or upper arms (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt [*see figure below*]).

Table 1 has specific dosing guidelines for when the unit-dose tubes or packets are used.

Table 1: Specific Dosing Guideline for Using the Unit-Dose Tubes or Packets

Prescribed Daily Dose	Number of Unit-Dose Tubes or Packets	Application Method
50 mg testosterone	One unit-dose tube or packet (once daily)	Apply one unit-dose tube or packet to one upper arm and shoulder.
100 mg testosterone	Two unit-dose tubes or packets (once daily)	Apply one unit-dose tube or packet to one upper arm and shoulder and then apply one unit-dose tube or packet to the opposite upper arm and shoulder.

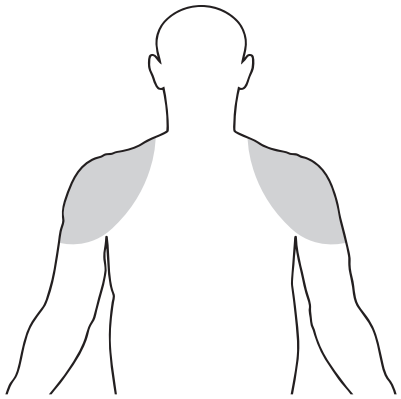
Multi-Dose Metered Pump

Patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. 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. Table 2 has specific dosing guidelines for when the metered pump is used.

Table 2: Specific Dosing Guidelines for Using the Multi-Dose Pump

Prescribed Daily Dose	Number of Pump Actuations	Application Method
50 mg testosterone	4 (once daily)	Apply 4 pump actuations to one upper arm and shoulder
100 mg testosterone	8 (once daily)	Apply 4 pump actuations to one upper arm and shoulder and then apply 4 pump actuations to the opposite upper arm and shoulder

The prescribed amount of product should be delivered directly into the palm of the hand and immediately applied to the shoulders and/or upper arms (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt [*see figure below*]).



Do not apply Vogelxo to the genitals or to the abdomen.

Application sites should be allowed to dry completely prior to dressing.

Hands should be washed thoroughly with soap and water after Vogelxo has been applied.

Avoid fire, flame or smoking during the application of Vogelxo until the Vogelxo has dried *[see Warnings and Precautions (5.2, 5.14)]*.

In order to prevent transfer to another person, clothing should be worn to cover the application sites. If direct skin-to-skin contact of the application site(s) with another person is anticipated, the application sites must be washed thoroughly with soap and water *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

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

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

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using Vogelxo.
- Vogelxo should only be applied to the upper arms and shoulders. 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 Vogelxo.
- 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 direct skin-to-skin contact of the application site(s) with another person 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 Vogelxo 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

Vogelxo (testosterone) gel is a clear to translucent hydroalcoholic topical gel for topical use available in unit-dose tubes, unit-dose packets, and multiple-dose metered pumps. Each tube or packet provides 50 mg testosterone in 5 g of gel. One pump actuation delivers 12.5 mg testosterone in 1.25 g of gel (4 actuations = 50 mg testosterone).

4 CONTRAINDICATIONS

- Vogelxo is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1)]*.
- Vogelxo is contraindicated in women who are or may become pregnant, or who are breastfeeding. Vogelxo may cause fetal harm when administered to a pregnant woman. Vogelxo 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 Vogelxo. If a pregnant woman is exposed to Vogelxo, 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

- Men 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)]*.

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 the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using Vogelxo *[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 Vogelxo. Evaluate patients who report signs and 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 Vogelxo and initiate appropriate workup and management *[see Adverse Reactions (6.2)]*.

5.5 Use in Women
Due to lack of controlled evaluations in women and potential virilizing effects, Vogelxo is not indicated for use in women.

5.6 Potential for Adverse Effects on Spermatogenesis
With large doses of exogenous androgens, including Vogelxo, 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.

5.7 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, which elevate blood levels for prolonged periods, has produced multiple hepatic adenomas. Vogelxo is not known to produce these adverse effects. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (e.g., jaundice). If these occur, promptly discontinue Vogelxo while the cause is evaluated.

5.8 Edema
Androgens, including Vogelxo, 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. In addition to discontinuation of the drug, diuretic therapy may be required.

5.9 Gynecomastia
Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism *[see Adverse Reactions (6.1)]*.

5.10 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.

5.11 Lipids
Changes in the serum lipid profile may occur. Monitor the lipid profile periodically, particularly after starting testosterone therapy and after any dose increases.

5.12 Hypercalcemia
Androgens, including Vogelxo, 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.

5.13 Decreased Thyroxine-binding Globulin
Androgens, including Vogelxo, may decrease concentrations of thyroxine-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.14 Flammability
Alcohol-based products, including Vogelxo, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the Vogelxo 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.

In a controlled clinical study, 304 patients were treated with testosterone gel 50 mg or 100 mg or placebo gel for up to 90 days. Two hundred-five (205) patients received testosterone gel 50 mg or 100 mg daily and 99 patients received placebo. Subjects could be counted in both testosterone gel treatment groups if they received both 50 mg and 100 mg at different points in the study and experienced an adverse reaction at both dose levels. Adverse reactions reported by ≥1% of the testosterone gel patients and greater than placebo are listed in Table 3.

Table 3: Incidence of Adverse Reactions (Reported by ≥1% of the Testosterone Gel Patients and Greater than Placebo) in the Controlled Clinical Trial Through 90 Days

Event	Testosterone Gel 50 mg (n=103)	Testosterone Gel 100 mg (n=149)	Placebo (n=99)
Application Site Reactions	2%	4%	3%
Blood Pressure Increased	1%	1%	0%
Gynecomastia	1%	0%	0%
Headache	1%	1%	0%
Hematocrit/Hemoglobin Increased	1%	2%	0%
Hot Flushes	1%	0%	0%
Insomnia	1%	0%	0%
Mood Swings	1%	0%	0%
Smell Disorder	1%	0%	0%
Spontaneous Penile Erection	1%	0%	0%
Taste Disorder	1%	1%	0%

The following adverse reactions occurred in fewer than 1% of patients but were greater in testosterone gel groups compared to the placebo group: activated partial thromboplastin time prolonged, blood creatinine increased, prothrombin time prolonged, appetite increased, sensitive nipples, and acne.

In this clinical trial of testosterone gel, six patients had adverse events that led to their discontinuation. These events included: depression with suicidal ideation, urinary tract infection, mood swings and hypertension. No testosterone gel patients discontinued due to skin reaction. In one foreign Phase 3 trial, one subject discontinued due to a skin-related adverse event.

In the pivotal U.S. and European Phase 3 trials combined, at the 50 mg dosage strength, the percentage of subjects reporting clinically notable increases in hematocrit or hemoglobin were similar to placebo. However, in the 100 mg dose group, 2.3% and 2.8% of patients had a clinically notable increase in hemoglobin (≥ 19 g/dL) or hematocrit (≥ 58%), respectively, compared to 1.0% and 1.5% of patients in the placebo group, respectively.

In the combined U.S. and European open label extension studies, approximately 140 patients received testosterone gel for at least 6 months. The results from these studies are consistent with those reported for the U.S. controlled clinical trial.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of testosterone gel products. 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 postmarketing surveillance of testosterone gel products. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or of 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 fabrics, such as towels and sheets *[see Warnings and Precautions (5.2)]*.

Vascular Disorders:
Venous thromboembolism *[see Warnings and Precautions (5.4)]*.

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 necessitate a decrease in the dose of anti-diabetic medication.

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 warfarin, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids
The concurrent use of testosterone with 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: Vogelxo is contraindicated in pregnant women or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens, such as testosterone, may result in varying degrees of virilization. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers
Although it is not known how much testosterone transfers into human milk, Vogelxo is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants.

8.4 Pediatric Use
The safety and efficacy of Vogelxo in pediatric patients less than 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 is insufficient long-term safety data in geriatric patients to assess the potentially increased risks of cardiovascular disease and prostate cancer *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment
No studies were conducted in patients with renal impairment.

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
Vogelxo 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

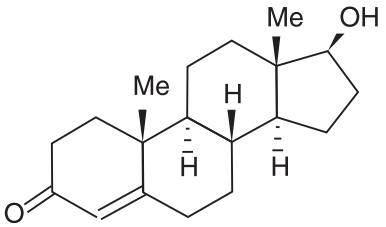
10 OVERDOSAGE
There were no reports of overdose in the testosterone gel clinical trials. There is a single report in the literature of acute overdosage after injection of testosterone enanthate. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident.

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

11 DESCRIPTION
Vogelxo (testosterone) gel, for topical use is a clear to translucent hydroalcoholic topical gel containing testosterone, an androgen. Vogelxo provides continuous transdermal delivery of testosterone for 24 hours, following a single application to intact, clean, dry skin of the shoulders and/or upper arms.

Vogelxo is available in unit-dose tubes, unit-dose packets, and a metered-dose pump. One 5-g or two 5-g tubes/packets of Vogelxo contains 50 mg or 100 mg of testosterone, respectively. One pump actuation dispenses 1.25 g of gel, which contains 12.5 mg of testosterone. Four pump actuations or eight pump actuations contain 50 mg or 100 mg of testosterone, respectively. Each metered-dose pump container is capable of dispensing 60 pump actuations.

The active pharmacological ingredient in Vogelxo is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-ß hydroxyandrost-4-en-3-one. The structural formula is shown in the following figure:



Testosterone ($C_{19}H_{28}O_2$) MW: 288.42

Inactive ingredients in Vogelxo are carbomer copolymer Type B, carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerin, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, and tromethamine.

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 the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution.

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

12.2 Pharmacodynamics
No specific pharmacodynamic studies were conducted using Vogelxo.

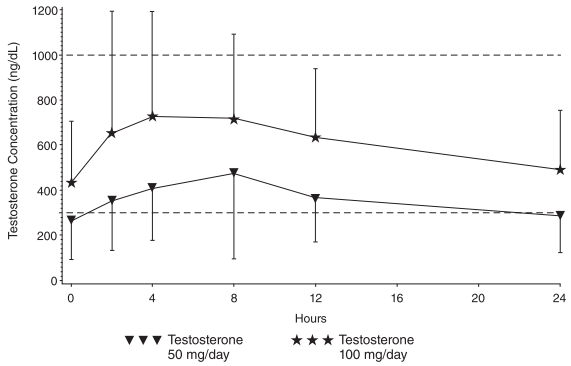
12.3 Pharmacokinetics
In a single-dose, replicate crossover clinical study evaluating 58 hypogonadal males, the serum testosterone exposures (AUC_{0-24} and AUC_{0-t}) and maximum testosterone concentration (C_{max}) following a topical administration of 100 mg testosterone administration as a 2 X 5 g Vogelxo tubes (applied to the shoulders/upper arms) were bioequivalent to those following a topical administration of an approved testosterone gel product.

Absorption
Testosterone gel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (e.g., 300 – 1000 ng/dL) seen in healthy men. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone applied on the skin surface is absorbed into the systemic circulation during a 24-hour period.

Single Dose
In a single dose, replicate crossover study, when Vogelxo 100 mg was applied, absorption of testosterone into the blood continued for the entire 24 hour dosing period. The average (± SD) AUC_{0-24} and AUC_{0-t} and C_{max} were 6625 (±3671) ng•hr/dL, 10425 (±5521) ng•hr/dL, and 573 (±284) ng/dL, respectively.

Multiple Dose
With single daily applications of testosterone gel 50 mg and 100 mg, follow-up measurements at 30 and 90 days after starting treatment have confirmed that serum testosterone and DHT concentrations are generally maintained within the normal range.
Figure 1 summarizes the 24-hour pharmacokinetic profile of testosterone for patients maintained on testosterone gel 50 mg or testosterone gel 100 mg for 30 days.

Figure 1
Mean Steady-State Serum Testosterone (±SD) (ng/dL) Concentrations on Day 30 in Patients Applying Testosterone Once Daily



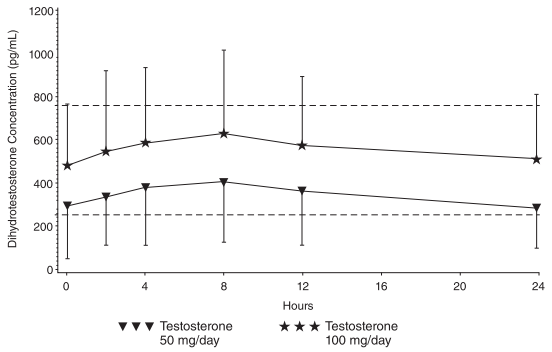
The average daily testosterone concentration produced by testosterone gel 100 mg at Day 30 was 612 (± 286) ng/dL and by testosterone gel 50 mg at Day 30 was 365 (±187) ng/dL.

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

Metabolism
Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT. The average daily DHT concentration produced by testosterone gel 100 mg at Day 30 was 555 (± 293) pg/mL and by testosterone gel 50 mg at Day 30 was 346 (± 212) pg/mL.

Figure 2 summarizes the 24-hour pharmacokinetic profile of DHT for patients maintained on testosterone gel 50 mg or testosterone gel 100 mg for 30 days.

Figure 2
Mean Steady-State Serum Dihydrotestosterone (±SD) (pg/mL) Concentrations on Day 30 in Patients Applying Testosterone Once Daily



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

Potential for Transfer from Male Patients to Female Partners
The potential for dermal testosterone transfer following Vogelxo use was evaluated in a clinical study between males dosed with Vogelxo and their untreated female partners. Two (2) hours after application of 50 mg of testosterone from 5 g of Vogelxo to upper arm and shoulder of one side by the male subjects, the couples (N = 48 couples) engaged in a 15 minute session of skin-to-skin contact. 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 2.8 and 4 times greater than their mean baseline values, respectively. When a shirt covered the application site or the application site was washed, study results showed less than 10% increase in testosterone AUC_{0-24} and C_{max}, compared to baseline in these females.

Effect of Hand Washing
In a clinical study conducted to evaluate the effect of hand washing on the residual amount of testosterone, 36 healthy male subjects received 50 mg of testosterone from 5 g of Vogelxo 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 water immediately after drug application. Then the hand was allowed to air dry or patted dry with a cloth towel. A skin swab sample was collected and analyzed for testosterone content. A mean (SD) of 0.16 (0.46) to 0.65(1.03) µg of residual testosterone (i.e., 99% reduction compared to when hands were not washed) was recovered after washing hands with liquid soap and warm water.

Effect of Showering
The effect of showering (with mild soap) at 1, 2 and 6 hours post application of testosterone gel 100 mg was evaluated in a clinical trial in 12 men. The study demonstrated that the overall effect of washing was to decrease testosterone concentrations; however, when washing occurred two or more hours post drug application, serum testosterone concentrations remained within the normal range.

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 Study in Hypogonadal Males

Testosterone gel was evaluated in a randomized multicenter, multi-dose, active and placebo controlled 90-day study in 406 adult males with morning testosterone levels ≤300 ng/dL. The study was double-blind for the doses of testosterone gel and placebo, but open label for the non-scrotal testosterone transdermal system. During the first 60 days, patients were evenly randomized to testosterone gel 50 mg, testosterone gel 100 mg, placebo gel, or testosterone transdermal system. At Day 60, patients receiving testosterone gel were maintained at the same dose, or were titrated up or down within their treatment group, based on 24-hour averaged serum testosterone concentration levels obtained on Day 30.

Of 192 hypogonadal men who were appropriately titrated with testosterone gel and who had sufficient data for analysis, 74% achieved an average serum testosterone level within the normal range (300 to 1,000 ng/dL) on treatment Day 90.

Table 4 summarizes the mean testosterone concentrations on Day 30 for patients receiving testosterone gel 50 mg or 100 mg.

Table 4: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30

	Testosterone gel 50 mg n=94	**Testosterone gel 100 mg n=95**	**Placebo gel n=93**
C_{avg} (ng/dL)	365 ± 187	612 ± 286	216 ± 79
C_{max} (ng/dL)	538 ± 371	897 ± 565	271 ± 110
C_{min} (ng/dL)	223 ± 126	394 ±189	164 ± 64

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Vogelxo is supplied in unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg testosterone in 5 g of gel.

Vogelxo is also supplied in a metered-dose pump that delivers 12.5 mg of testosterone per complete pump actuation. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations. Each pump actuation delivers 1.25 g of gel. The metered-dose pump is supplied in cartons of 2.

Vogelxo is available as follows:

NDC Number	Strength	Package Size
0245-0871-05	50 mg of testosterone	30 tubes (5 g of gel per tube)
0245-0871-65	50 mg of testosterone	1 tube (5 g of gel per tube)
0245-0871-35	50 mg of testosterone	30 packets (5 g of gel per packet)
0245-0871-89	50 mg of testosterone	1 packet (5 g of gel per packet)
0245-0872-42	12.5 mg of testosterone per pump actuation	2 x 75 g pumps (each pump dispenses 60 metered 1.25 g of gel)

16.2 Storage
Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

16.3 Handling and Disposal
Used Vogelxo tubes, packets or pumps should be discarded in household trash in a manner that prevents accidental exposure of women, children, or pets *[see Boxed Warning and Warnings and Precautions (5.2)]*. Contents are flammable *[see Warnings and Precautions (5.14)]*.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Men with Known or Suspected Carcinoma of the Breast or Prostate
Men with known or suspected prostate or breast cancer should not use Vogelxo *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

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 products 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 Vogelxo should be brought to the attention of a healthcare provider
- Vogelxo 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 Vogelxo in men *[see Medication Guide]*

- **Children and women should avoid contact with unwashed or unclothed application site(s) of men using Vogelxo**
- Patients using Vogelxo should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water immediately 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 Vogelxo 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)]*.

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 the urine stream, passing urine many times during the day, having an urge to go the bathroom right away, having a urine accident, or being unable to pass urine or 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

Patients Should Be Advised of the Following Instructions for Use

- **Read the Medication Guide before starting Vogelxo therapy and reread it each time the prescription is renewed.**
- **Vogelxo should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women.**
- **Keep Vogelxo out of the reach of children. The package is not child resistant.**
- **Vogelxo 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.
- Vogelxo is prescribed to meet the patient's specific needs; therefore, the patient should never share Vogelxo with anyone.
- Vogelxo should be applied topically once daily at approximately the same time each day to clean dry skin of the shoulders and/or upper arms.
- Vogelxo should not be applied to the scrotum, penis, or abdomen.
- Wait 2 hours before washing or swimming following application of Vogelxo. This will ensure that the greatest amount of Vogelxo is absorbed.

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Maple Grove, MN 55369

MADE IN CANADA

Revised 06/2014

MEDICATION GUIDE
VOGELXO™ (voh-JELKS-oh), CIII
(testosterone) gel

Read this Medication Guide that comes with Vogelxo 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 Vogelxo?

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

   Vogelxo can transfer from your body to others.
2. **Women and children should avoid contact with the unwashed or unclothed area where Vogelxo has been applied to your skin.**
   Stop using Vogelxo 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 Vogelxo.
   Signs and symptoms of exposure to Vogelxo 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 Vogelxo in women may include:
   - changes in body hair
   - a large increase in acne

   To lower the risk of transfer of Vogelxo from your body to others, you should follow these important instructions:
   - Apply Vogelxo **only** to the areas of your shoulders and upper arms that will be covered by a short sleeve T-shirt.
   - Wash your hands **right away** with soap and water after applying Vogelxo.
   - 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 Vogelxo application area, that area on the woman or child should be washed well with soap and water right away.**

What is Vogelxo?
Vogelxo is a prescription medicine that contains testosterone. Vogelxo is used to treat adult males who have low or no testosterone and with conditions associated with low or no testosterone.
Your healthcare provider will test your blood before you start and while you use Vogelxo.
It is not known if Vogelxo is safe or effective in children younger than 18 years old. Improper use of Vogelxo may affect bone growth in children.
Vogelxo is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your Vogelxo in a safe place to protect it. Never give your Vogelxo to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and it is against the law.
Vogelxo is not meant for use in women.

Who should not use Vogelxo?
Do not use Vogelxo if you:
- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breastfeeding. Vogelxo may harm your unborn or breastfeeding baby.
- Women who are pregnant or who may become pregnant should avoid contact with the area of skin where Vogelxo has been applied.

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

What should I tell my healthcare provider before using Vogelxo?
Before you use Vogelxo, 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

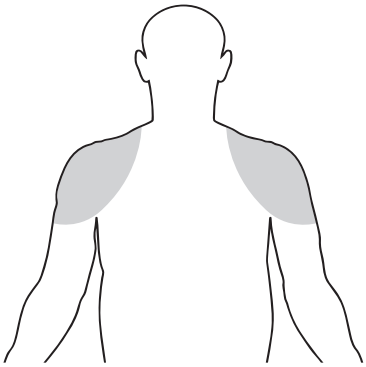
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Vogelxo and certain other medicines you take can affect each other. Especially, tell your healthcare provider if you take:
- insulin
- medicines that decrease blood clotting
- corticosteroids

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 Vogelxo?
- It is important that you apply Vogelxo exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much Vogelxo to apply and when to apply it.
- Your healthcare provider may change your Vogelxo dose. **Do not** change your Vogelxo dose without talking to your healthcare provider.
- **Vogelxo is to be applied only to the areas of your shoulders and upper arms that will be covered by a short sleeve t-shirt. Do not** apply Vogelxo to any other parts of your body such as your penis, scrotum, or stomach area (abdomen).
- Apply Vogelxo at the same time each day. Vogelxo should be applied after showering or bathing.
- **Wash your hands right away with soap and water** after applying Vogelxo.
- Avoid showering, swimming, or bathing for at least 2 hours after you apply Vogelxo.
- Vogelxo is flammable until dry. Let Vogelxo dry before smoking or going near an open flame.
- Let the application areas dry before putting on a t-shirt.

Applying Vogelxo:
Vogelxo comes in tubes, packets, or in a pump.
- **Before applying Vogelxo, make sure that your shoulders and upper arms are clean, dry, and there is no broken skin.**
- The application sites for Vogelxo are the shoulders and the upper arms that will be covered by a short sleeve t-shirt (See Figure A).

Figure A



If you are using Vogelxo tubes:
- Remove the cap from the tube and use the top of the cap to puncture the metal seal on the top of the tube.
- Squeeze from the bottom of the tube to the top.
- Squeeze all of the Vogelxo out of the tube into the palm of your hand.
- Apply Vogelxo to the application site. Rub the gel onto your skin for several seconds. Let the application site dry for a few minutes before putting on a T-shirt.
- **Wash your hands with soap and water right away.**
- Put the cap back on the tube.

If you are using Vogelxo packets:
- Tear open the packet completely at the notch on the top edge. Squeeze from the bottom of the packet to the top.
- Squeeze all of the Vogelxo out of the packet into the palm of your hand. Apply Vogelxo to the application site. Rub the gel onto your skin for several seconds. Let the application site dry for a few minutes before putting on a T-shirt.
- **Wash your hands with soap and water right away.**

If you are using the Vogelxo pump:
- Before using a new bottle of Vogelxo for the **first time**, you will need to prime the pump. To prime the Vogelxo pump, remove the cap and slowly push the pump all the way down 3 times.
- **Do not** use any Vogelxo that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your Vogelxo 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. Your healthcare provider will tell you the number of times to press the pump for each dose.
- Apply Vogelxo to the application site. Rub the gel onto your skin for several seconds. Let the application site dry for a few minutes before putting on a T-shirt.

- **Wash your hands with soap and water right away.**
- Put the cap back on the pump.

What are the possible side effects of Vogelxo?
Vogelxo can cause serious side effects including:
- See **"What is the most important information I should know about Vogelxo?"**
- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using Vogelxo.** 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 Vogelxo.
- **Blood clots in your legs or lungs.** Signs and symptoms of a blood clot in your legs can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **In large doses Vogelxo may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Having 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 Vogelxo include:
- skin irritation where Vogelxo is applied
- increased red blood cell count
- headache
- increased blood pressure

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 Vogelxo. For more information, ask your healthcare provider or pharmacist.
Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Vogelxo?
- Store Vogelxo between 68ºF to 77ºF (20ºC to 25ºC).
- Safely throw away used Vogelxo containers in household trash. Be careful to prevent accidental exposure of children or pets.
- Keep Vogelxo away from fire.

Keep Vogelxo and all medicines out of the reach of children.

General information about the safe and effective use of Vogelxo.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Vogelxo for a condition for which it was not prescribed. Do not give Vogelxo to other people, even if they have the same symptoms that you have. It may harm them.
This Medication Guide summarizes the most important information about Vogelxo. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Vogelxo that is written for health professionals.
For more information, go to www.upsher-smith.com or call 1-888-650-3789.

What are the ingredients in Vogelxo?
Active ingredient: testosterone
Inactive ingredients: carbomer copolymer Type B, carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerin, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, and tromethamine

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

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Maple Grove, MN 55369

MADE IN CANADA

Issued 6/2014
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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)**

----------INDICATIONS AND USAGE----------

Testosterone gel is an androgen indicated for testosterone 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 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----------

- Recommended starting dose for adult males: 50 mg of testosterone (one tube or one packet or 4 pump actuations) applied topically once daily at approximately the same time each day. (2.1)
- Apply to clean, dry, intact skin of the shoulders and/or upper arms. Do not apply testosterone gel to the genitals or abdomen. (2.1, 2.2)
- If morning pre-dose serum testosterone concentration is below the normal range, increase dose to 100 mg. (2.1)
- Pre-dose serum testosterone concentration should be assessed periodically. (2.1)
- Patients should wash hands with soap and water immediately after applying testosterone gel and cover application site(s) with clothing after gel has dried. Wash the application sites 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----------

Topical Gel available as:

- 50 mg of testosterone in a unit-dose tube. (3)
- 50 mg of testosterone in a unit-dose packet. (3)
- 12.5 mg of testosterone per one pump actuation in a metered-dose pump. (3)

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

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

----------WARNINGS AND PRECAUTIONS----------

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to testosterone gel. Secondary exposure to testosterone can produce signs of virilization. Testosterone gel should be discontinued until the cause of virilization is identified. (5.2)
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Exogenous administration of androgens may lead to azoospermia. (5.6)
- Edema, with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.8, 6.2)
- Sleep apnea may occur in those with risk factors. (5.10)
- Monitor prostate specific antigen (PSA), hematocrit, and lipid concentrations periodically. (5.1, 5.3, 5.11)
- Testosterone gel is flammable until dry. (5.14)

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

- Most common adverse reactions (incidence ≥ 2% of the testosterone gel patients and greater than placebo) are application site reactions and increased hematocrit. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UPSHER-SMITH LABORATORIES, INC. at 1-855-899-9180 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 in patients taking warfarin. (7.2)
- Use of testosterone with 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----------

Geriatric Patients: There are insufficient long-term safety data to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2014

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

1 INDICATIONS AND USAGE

Testosterone gel is indicated for testosterone 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 (follicle-stimulating hormone [FSH], luteinizing hormone [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.

Limitations of use:

- 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 *[see Dosage and Administration (2) and 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 (one tube, one packet, or 4 pump actuations) applied topically once daily at approximately the same time each day to clean, dry intact skin of the shoulders and/or upper arms.

Dose Adjustment

To ensure proper dosing, serum testosterone concentrations should be measured. Morning, pre-dose serum testosterone concentrations should be measured approximately 14 days after initiation of therapy to ensure proper serum testosterone concentrations are achieved. If the serum testosterone concentration is below the normal range (300 ng/dL to 1,000 ng/dL), the daily testosterone gel dose may be increased from 50 mg testosterone (one tube, one packet, or 4 pump actuations) to 100 mg of testosterone (two tubes, two packets, or 8 pump actuations) once daily.

The maximum recommended dose of testosterone gel is 100 mg once daily.

2.2 Administration Instructions

Unit-Dose Tube or Packet

Upon opening the tube or packet the entire contents should be squeezed into the palm of the hand and immediately applied to the shoulders and/or upper arms (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt [*see figure below*]).

Table 1 has specific dosing guidelines for when the unit-dose tubes or packets are used.

Table 1: Specific Dosing Guideline for Using the Unit-Dose Tubes or Packets

Prescribed Daily Dose	Number of Unit-Dose Tubes or Packets	Application Method
50 mg testosterone	One unit-dose tube or packet (once daily)	Apply one unit-dose tube or packet to one upper arm and shoulder.
100 mg testosterone	Two unit-dose tubes or packets (once daily)	Apply one unit-dose tube or packet to one upper arm and shoulder and then apply one unit-dose tube or packet to the opposite upper arm and shoulder.

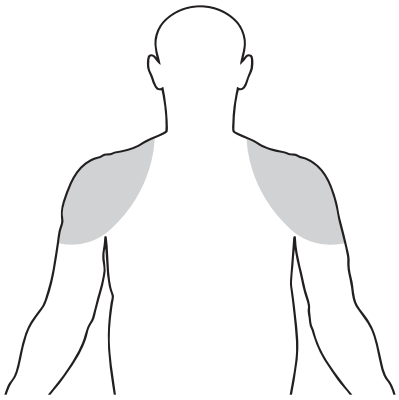
Multi-Dose Metered Pump

Patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. 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. Table 2 has specific dosing guidelines for when the metered pump is used.

Table 2: Specific Dosing Guidelines for Using the Multi-Dose Pump

Prescribed Daily Dose	Number of Pump Actuations	Application Method
50 mg testosterone	4 (once daily)	Apply 4 pump actuations to one upper arm and shoulder
100 mg testosterone	8 (once daily)	Apply 4 pump actuations to one upper arm and shoulder and then apply 4 pump actuations to the opposite upper arm and shoulder

The prescribed amount of product should be delivered directly into the palm of the hand and immediately applied to the shoulders and/or upper arms (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt [*see figure below*]).



Do not apply testosterone gel to the genitals or to the abdomen.

Application sites should be allowed to dry completely prior to dressing.

Hands should be washed thoroughly with soap and water after testosterone gel has been applied.

Avoid fire, flame or smoking during the application of testosterone gel until the gel has dried *[see Warnings and Precautions (5.2, 5.14)]*.

In order to prevent transfer to another person, clothing should be worn to cover the application sites. If direct skin-to-skin contact of the application site(s) with another person is anticipated, the application sites must be washed thoroughly with soap and water *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

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

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. 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 any situation in which direct skin-to-skin contact of the application site(s) with another person 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 is a clear to translucent hydroalcoholic topical gel for topical use available in unit-dose tubes, unit-dose packets, and multiple-dose metered pumps. Each tube or packet provides 50 mg testosterone in 5 g of gel. One pump actuation delivers 12.5 mg testosterone in 1.25 g of gel (4 actuations = 50 mg testosterone).

4 CONTRAINDICATIONS

- Testosterone gel is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1)]*.
- 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

- Men 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)]*

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 the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using testosterone gel *[see Dosage and Administration (2.2), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

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

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

5.4 Venous Thromboembolism
There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as testosterone gel. Evaluate patients who report signs and 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 Use in Women
Due to lack of controlled evaluations in women and potential virilizing effects, testosterone gel is not indicated for use in women.

5.6 Potential for Adverse Effects on Spermatogenesis
With 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.

5.7 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, which elevate blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone gel is not known to produce these adverse effects. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (e.g., jaundice). If these occur, promptly discontinue testosterone gel while the cause is evaluated.

5.8 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. In addition to discontinuation of the drug, diuretic therapy may be required.

5.9 Gynecomastia
Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism *[see Adverse Reactions (6.1)]*.

5.10 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.

5.11 Lipids
Changes in the serum lipid profile may occur. Monitor the lipid profile periodically, particularly after starting testosterone therapy and after any dose increases.

5.12 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.

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

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

In a controlled clinical study, 304 patients were treated with testosterone gel 50 mg or 100 mg or placebo gel for up to 90 days. Two hundred-five (205) patients received testosterone gel 50 mg or 100 mg daily and 99 patients received placebo. Subjects could be counted in both testosterone gel treatment groups if they received both 50 mg and 100 mg at different points in the study and experienced an adverse reaction at both dose levels. Adverse reactions reported by ≥1% of the testosterone gel patients and greater than placebo are listed in Table 3.

Table 3: Incidence of Adverse Reactions (Reported by ≥1% of the Testosterone Gel Patients and Greater than Placebo) in the Controlled Clinical Trial Through 90 Days

Event	Testosterone Gel 50 mg (n=103)	Testosterone Gel 100 mg (n=149)	Placebo (n=99)
Application Site Reactions	2%	4%	3%
Blood Pressure Increased	1%	1%	0%
Gynecomastia	1%	0%	0%
Headache	1%	1%	0%
Hematocrit/Hemoglobin Increased	1%	2%	0%
Hot Flushes	1%	0%	0%
Insomnia	1%	0%	0%
Mood Swings	1%	0%	0%
Smell Disorder	1%	0%	0%
Spontaneous Penile Erection	1%	0%	0%
Taste Disorder	1%	1%	0%

The following adverse reactions occurred in fewer than 1% of patients but were greater in testosterone gel groups compared to the placebo group: activated partial thromboplastin time prolonged, blood creatinine increased, prothrombin time prolonged, appetite increased, sensitive nipples, and acne.

In this clinical trial of testosterone gel, six patients had adverse events that led to their discontinuation. These events included: depression with suicidal ideation, urinary tract infection, mood swings and hypertension. No testosterone gel patients discontinued due to skin reaction. In one foreign Phase 3 trial, one subject discontinued due to a skin-related adverse event.

In the pivotal U.S. and European Phase 3 trials combined, at the 50 mg dosage strength, the percentage of subjects reporting clinically notable increases in hematocrit or hemoglobin were similar to placebo. However, in the 100 mg dose group, 2.3% and 2.8% of patients had a clinically notable increase in hemoglobin (≥ 19 g/dL) or hematocrit (≥ 58%), respectively, compared to 1.0% and 1.5% of patients in the placebo group, respectively.

In the combined U.S. and European open label extension studies, approximately 140 patients received testosterone gel for at least 6 months. The results from these studies are consistent with those reported for the U.S. controlled clinical trial.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of testosterone gel products. 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 postmarketing surveillance of testosterone gel products. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or of 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 fabrics, such as towels and sheets *[see Warnings and Precautions (5.2)]*.

Vascular Disorders:
Venous thromboembolism *[see Warnings and Precautions (5.4)]*.

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 necessitate a decrease in the dose of anti-diabetic medication.

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 warfarin, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids
The concurrent use of testosterone with 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: Testosterone gel is contraindicated in pregnant women or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens, such as testosterone, may result in varying degrees of virilization. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers
Although it is not known how much testosterone transfers into human milk, testosterone gel is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants.

8.4 Pediatric Use
The safety and efficacy of testosterone gel in pediatric patients less than 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 is insufficient long-term safety data in geriatric patients to assess the potentially increased risks of cardiovascular disease and prostate cancer *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment
No studies were conducted in patients with renal impairment.

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

9 DRUG ABUSE AND DEPENDENCE

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

9.2 Abuse
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

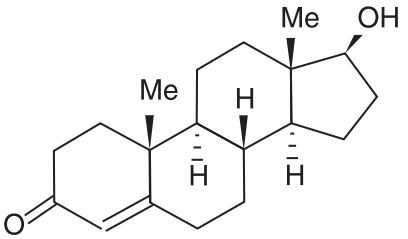
10 OVERDOSAGE
There were no reports of overdose in the testosterone gel clinical trials. There is a single report in the literature of acute overdosage after injection of testosterone enanthate. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular 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, for topical use is a clear to translucent hydroalcoholic topical gel containing testosterone, an androgen. Testosterone gel provides continuous transdermal delivery of testosterone for 24 hours, following a single application to intact, clean, dry skin of the shoulders and/or upper arms.

Testosterone gel is available in unit-dose tubes, unit-dose packets, and a metered-dose pump. One 5-g or two 5-g tubes/packets of testosterone gel contains 50 mg or 100 mg of testosterone, respectively. One pump actuation dispenses 1.25 g of gel, which contains 12.5 mg of testosterone. Four pump actuations or eight pump actuations contain 50 mg or 100 mg of testosterone, respectively. Each metered-dose pump container is capable of dispensing 60 pump actuations.

The active pharmacological ingredient in testosterone gel is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-ß hydroxyandrost-4-en-3-one. The structural formula is shown in the following figure:



Testosterone ($C_{19}H_{28}O_2$) MW: 288.42

Inactive ingredients in testosterone gel are carbomer copolymer Type B, carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerin, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, and tromethamine.

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 the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution.

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

12.2 Pharmacodynamics
No specific pharmacodynamic studies were conducted using testosterone gel.

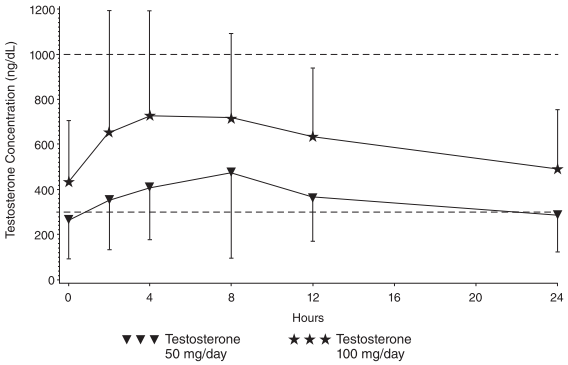
12.3 Pharmacokinetics
In a single-dose, replicate crossover clinical study evaluating 58 hypogonadal males, the serum testosterone exposures ($AUC_{0\text{-}24}$ and $AUC_{0\text{-}t}$) and maximum testosterone concentration (C_{max}) following a topical administration of 100 mg testosterone administration as a 2 X 5 g testosterone gel tubes (applied to the shoulders/upper arms) were bioequivalent to those following a topical administration of an approved testosterone gel product.

Absorption
Testosterone gel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (e.g., 300 – 1000 ng/dL) seen in healthy men. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone applied on the skin surface is absorbed into the systemic circulation during a 24-hour period.

Single Dose
In a single dose, replicate crossover study, when testosterone gel 100 mg was applied, absorption of testosterone into the blood continued for the entire 24 hour dosing period. The average (± SD) $AUC_{0\text{-}24}$ and $AUC_{0\text{-}t}$ and C_{max} were 6625 (±3671) ng•hr/dL, 10425 (±5521) ng•hr/dL, and 573 (±284) ng/dL, respectively.

Multiple Dose
With single daily applications of testosterone gel 50 mg and 100 mg, follow-up measurements at 30 and 90 days after starting treatment have confirmed that serum testosterone and DHT concentrations are generally maintained within the normal range.
Figure 1 summarizes the 24-hour pharmacokinetic profile of testosterone for patients maintained on testosterone gel 50 mg or testosterone gel 100 mg for 30 days.

Figure 1
Mean Steady-State Serum Testosterone (±SD) (ng/dL) Concentrations on Day 30 in Patients Applying Testosterone Once Daily



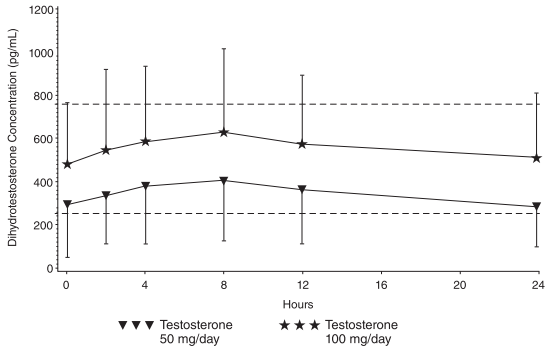
The average daily testosterone concentration produced by testosterone gel 100 mg at Day 30 was 612 (± 286) ng/dL and by testosterone gel 50 mg at Day 30 was 365 (±187) ng/dL.

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

Metabolism
Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT. The average daily DHT concentration produced by testosterone gel 100 mg at Day 30 was 555 (± 293) pg/mL and by testosterone gel 50 mg at Day 30 was 346 (± 212) pg/mL.

Figure 2 summarizes the 24-hour pharmacokinetic profile of DHT for patients maintained on testosterone gel 50 mg or testosterone gel 100 mg for 30 days.

Figure 2
Mean Steady-State Serum Dihydrotestosterone (±SD) (pg/mL) Concentrations on Day 30 in Patients Applying Testosterone Once Daily



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

Potential for 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 50 mg of testosterone from 5 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 session of skin-to-skin contact. 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 2.8 and 4 times greater than their mean baseline values, respectively. When a shirt covered the application site or the application site was washed, study results showed less than 10% increase in testosterone AUC_{0-24} and C_{max}, compared to baseline in these females.

Effect of Hand Washing
In a clinical study conducted to evaluate the effect of hand washing on the residual amount of testosterone, 36 healthy male subjects received 50 mg of testosterone from 5 g 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 water immediately after drug application. Then the hand was allowed to air dry or patted dry with a cloth towel. A skin swab sample was collected and analyzed for testosterone content. A mean (SD) of 0.16 (0.46) to 0.65(1.03) µg of residual testosterone (i.e., 99% reduction compared to when hands were not washed) was recovered after washing hands with liquid soap and warm water.

Effect of Showering
The effect of showering (with mild soap) at 1, 2 and 6 hours post application of testosterone gel 100 mg was evaluated in a clinical trial in 12 men. The study demonstrated that the overall effect of washing was to decrease testosterone concentrations; however, when washing occurred two or more hours post drug application, serum testosterone concentrations remained within the normal range.

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 Study in Hypogonadal Males
Testosterone gel was evaluated in a randomized multicenter, multi-dose, active and placebo controlled 90-day study in 406 adult males with morning testosterone levels ≤300 ng/dL. The study was double-blind for the doses of testosterone gel and placebo, but open label for the non-scrotal testosterone transdermal system. During the first 60 days, patients were evenly randomized to testosterone gel 50 mg, testosterone gel 100 mg, placebo gel, or testosterone transdermal system. At Day 60, patients receiving testosterone gel were maintained at the same dose, or were titrated up or down within their treatment group, based on 24-hour averaged serum testosterone concentration levels obtained on Day 30.

Of 192 hypogonadal men who were appropriately titrated with testosterone gel and who had sufficient data for analysis, 74% achieved an average serum testosterone level within the normal range (300 to 1,000 ng/dL) on treatment Day 90.

Table 4 summarizes the mean testosterone concentrations on Day 30 for patients receiving testosterone gel 50 mg or 100 mg.

Table 4: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30

	Testosterone gel 50 mg n=94	**Testosterone gel 100 mg n=95**	**Placebo gel n=93**
C_{avg} (ng/dL)	365 ± 187	612 ± 286	216 ± 79
C_{max} (ng/dL)	538 ± 371	897 ± 565	271 ± 110
C_{min} (ng/dL)	223 ± 126	394 ±189	164 ± 64

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Testosterone gel is supplied in unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg testosterone in 5 g of gel.

Testosterone gel is also supplied in a metered-dose pump that delivers 12.5 mg of testosterone per complete pump actuation. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations. Each pump actuation delivers 1.25 g of gel. The metered-dose pump is supplied in cartons of 2.

Testosterone gel is available as follows:

NDC Number	Strength	Package Size
0832-1120-05	50 mg of testosterone	30 tubes (5 g of gel per tube)
0832-1120-65	50 mg of testosterone	1 tube (5 g of gel per tube)
0832-1120-35	50 mg of testosterone	30 packets (5 g of gel per packet)
0832-1120-89	50 mg of testosterone	1 packet (5 g of gel per packet)
0832-1121-42	12.5 mg of testosterone per pump actuation	2 x 75 g pumps (each pump dispenses 60 metered 1.25 g of gel)

16.2 Storage
Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

16.3 Handling and Disposal
Used testosterone gel tubes, packets or pumps should be discarded in household trash in a manner that prevents accidental exposure of women, children, or pets *[see Boxed Warning and Warnings and Precautions (5.2)]*. Contents are flammable *[see Warnings and Precautions (5.14)]*.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Men with Known or Suspected Carcinoma of the Breast or Prostate

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

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 products 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 *[see Medication Guide]*

- **Children and women should avoid contact with unwashed or unclothed application site(s) of men using testosterone gel**
- Patients using testosterone gel should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water immediately 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)]*.

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 the urine stream, passing urine many times during the day, having an urge to go the bathroom right away, having a urine accident, or being unable to pass urine or 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

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. The package is not child resistant.**
- **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.
- Testosterone gel should be applied topically once daily at approximately the same time each day to clean dry skin of the shoulders and/or upper arms.
- Testosterone gel should not be applied to the scrotum, penis, or abdomen.
- Wait 2 hours before washing or swimming following application of testosterone gel. This will ensure that the greatest amount of testosterone gel is absorbed.

Manufactured for
USL PHARMA, INC.
Denver, CO 80223

MADE IN CANADA

Revised 06/2014

MEDICATION GUIDE
Testosterone (tes-TOS-te-rōn) 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 the areas of your shoulders and upper arms that will be covered by a short sleeve T-shirt.
   - 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 and with conditions associated with low or no testosterone. Your healthcare provider will test your blood before you start and while you use testosterone gel.
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 it 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 are breastfeeding. Testosterone gel may harm your unborn or breastfeeding 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 using 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

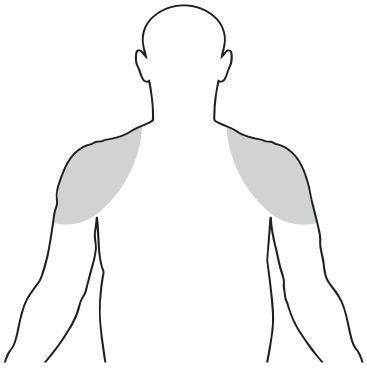
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Testosterone gel and certain other medicines you take can affect each other.
Especially, tell your healthcare provider if you take:
- insulin
- medicines that decrease blood clotting
- corticosteroids

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 only to the areas of your shoulders and upper arms 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, or stomach area (abdomen).
- Apply testosterone gel at the same time each day. 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 2 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 tubes, packets, or in a pump.
- **Before applying testosterone gel, make sure that your shoulders and upper arms are clean, dry, and there is no broken skin.**
- The application sites for testosterone gel are the shoulders and the upper arms that will be covered by a short sleeve t-shirt (See Figure A).

Figure A



If you are using testosterone gel tubes:
- Remove the cap from the tube and use the top of the cap to puncture the metal seal on the top of the tube.
- Squeeze from the bottom of the tube to the top.
- Squeeze all of the testosterone gel out of the tube into the palm of your hand.
- Apply testosterone gel to the application site. Rub the gel onto your skin for several seconds. Let the application site dry for a few minutes before putting on a T-shirt.
- **Wash your hands with soap and water right away.**
- Put the cap back on the tube.

If you are using testosterone gel packets:
- Tear open the packet completely at the notch on the top edge. 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. Rub the gel onto your skin for several seconds. Let the application site dry for a few minutes before putting on a T-shirt.
- **Wash your hands with soap and water right away.**

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, remove the cap and 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. Your healthcare provider will tell you the number of times to press the pump for each dose.
- Apply testosterone gel to the application site. Rub the gel onto your skin for several seconds. Let the application site dry for a few minutes before putting on a T-shirt.
- **Wash your hands with soap and water right away.**
- Put the cap back on the pump.

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 your legs or lungs.** Signs and symptoms of a blood clot in your legs can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **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.**
- **Having 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:
- skin irritation where testosterone gel is applied
- increased red blood cell count
- headache
- increased blood pressure

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 healthcare provider 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 containers 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 that you have. It may harm them.
This Medication Guide summarizes the most important information about testosterone gel. If you would like more information, talk with 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.upsher-smith.com or call 1-888-650-3789.

What are the ingredients in testosterone gel?
Active ingredient: testosterone
Inactive ingredients: carbomer copolymer Type B, carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerin, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, and tromethamine

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

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