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

TESTIM® (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 (5.1, 6.2)**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel (2.2, 5.1)**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.1, 17)**

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

Warnings and Precautions, Venous Thromboembolism (5.3)	07/2025
Warnings and Precautions, Blood Pressure Increases (5.5)	07/2025
Warnings and Precautions, Cardiovascular Risk (5.5) Removed	07/2025

INDICATIONS AND USAGE

TESTIM 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 (1)

Limitations of Use:
- Safety and efficacy of TESTIM in men with "age-related hypogonadism" have not been established. (1)
- Safety and efficacy of TESTIM in males less than 18 years old have not been established. (8.4)
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. (1, 12.3)

DOSAGE AND ADMINISTRATION

- Prior to initiating TESTIM, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range. (2)
- Recommended starting dose for adult males: 50 mg of testosterone (one tube) applied topically once daily. (2.1)
- Apply to clean, dry, intact skin of the shoulders and/or upper arms. Do NOT apply TESTIM to the genitals or abdomen. (2.1, 2.2)
- If morning pre-dose serum testosterone concentration is below 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 TESTIM and cover application site(s) with clothing after gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)
- TESTIM is not substitutable with other topical testosterone products. (2.1)

DOSAGE FORMS AND STRENGTHS

Topical gel: 50 mg of testosterone in a unit-dose tube (3)

CONTRAINDICATIONS

- Men with known carcinoma of the breast or known or suspected carcinoma of the prostate. (4, 5.4)
- Women who are pregnant. Testosterone may cause fetal harm. (4, 5.7, 8.1, 8.2)

WARNINGS AND PRECAUTIONS

- Potential for Secondary Exposure to Testosterone: Avoid unintentional exposure of women or children to TESTIM. Secondary exposure to testosterone can produce signs of virilization. TESTIM should be discontinued until the cause of virilization is identified. (5.1)
- Venous thromboembolism (VTE): 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. (5.3)
- Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer: Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.4)
- Blood Pressure Increases: Testosterone can increase blood pressure, which can increase cardiovascular risk over time. Measure blood pressure periodically. Not recommended for use in men with uncontrolled hypertension (5.5)
- Abuse of Testosterone: Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (5.6).
- Potential for Adverse Effects on Spermatogenesis
- Exogenous administration of androgens may lead to azoospermia. (5.8)
- Edema: Edema, with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.10, 6.2)
- Sleep apnea: Sleep apnea may occur in those with risk factors. (5.12)
- Monitor prostate specific antigen (PSA), hematocrit, and lipid concentrations periodically. (5.2, 5.4, 5.13)
- TESTIM is flammable until dry. (5.16)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Endo at 1-800-462-3636 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: 07/2025

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 (5.1) 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 (5.1)]*.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), and Patient Counseling Information (17)]*.**

1 INDICATIONS AND USAGE

TESTIM 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 concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Limitations of Use:

- Safety and efficacy of TESTIM in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.
- Safety and efficacy of TESTIM 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

Prior to initiating TESTIM, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosing and Dose Adjustment

The recommended starting dose of TESTIM is 50 mg of testosterone (one tube) applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms.

Dose Adjustment

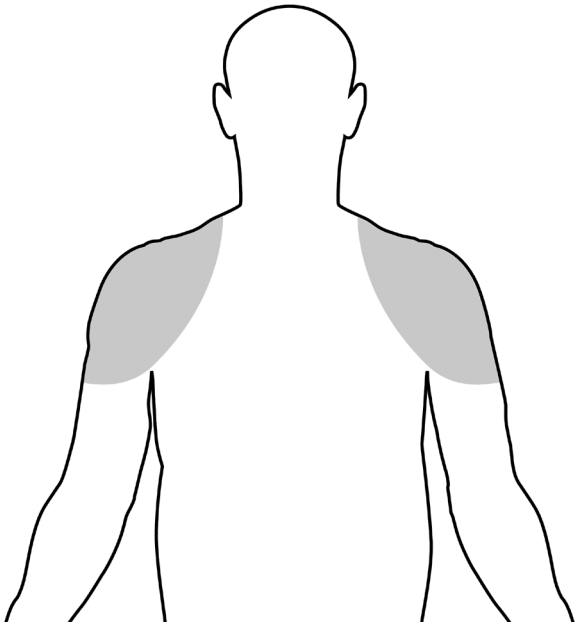
To ensure proper dosing, serum testosterone concentrations should be measured. Morning, pre-dose serum testosterone concentrations should be measured approximately 14 days after initiation of therapy to ensure proper serum testosterone concentrations are achieved. If the serum testosterone concentration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

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

The application site and dose of TESTIM are not substitutable with other topical testosterone products.

2.2 Administration Instructions

Upon opening the tube 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*). Do not apply TESTIM to the genitals or to the abdomen.



Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed thoroughly with soap and water after TESTIM has been applied. Avoid fire, flame or smoking during the application of TESTIM until the TESTIM has dried *[see Warnings and Precautions (5.1, 5.16)]*.

In order to prevent transfer to another person, wear clothing to cover the application sites. If direct skin-to-skin contact with another person is anticipated, the application sites must be washed thoroughly with soap and water *[see Warnings and Precautions (5.1) 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 TESTIM-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using TESTIM.
- TESTIM 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 TESTIM.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the gel has dried.
- Prior to situations in which direct skin-to-skin contact is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which TESTIM 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

TESTIM (testosterone gel) for topical use is available in a unit-dose tube. Each tube contains 50 mg testosterone in 5 g of gel.

4 CONTRAINDICATIONS

- TESTIM is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.4)]*.
- TESTIM is contraindicated in women who are pregnant. Testosterone can cause virilization of the female fetus when administered to a pregnant woman *[see Use in Specific Populations (8.1, 8.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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 TESTIM *[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.

5.2 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.

5.3 Venous Thromboembolism (VTE)

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 TESTIM.

In the Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) Study, a randomized, double-blind, placebo-controlled, cardiovascular (CV) outcomes study, compared to placebo, topical testosterone gel was associated with a numerically higher incidence of VTE (1.7% vs 1.2%) which included DVT (0.6% vs 0.5%) and PE events (0.9% vs 0.5%) *[see Adverse Reactions (6.1)]*.

Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with TESTIM and initiate appropriate workup and management *[see Adverse Reactions (6.2)]*.

5.4 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4)]*.

5.5 Blood Pressure Increases

TESTIM can increase blood pressure. In an ambulatory blood pressure monitoring (ABPM) study, TESTIM increased the mean systolic/diastolic blood pressure by 2.7/1.1 mm Hg from baseline after 16 weeks of treatment. In patients with hypertension on antihypertensive therapy, TESTIM increased the mean systolic/diastolic BP by 1.9/0.3 mm Hg from baseline. Blood pressure increases can increase cardiovascular (CV) risk over time.

The CV risk associated with topical testosterone gel was evaluated in TRAVERSE, a randomized, double-blind, placebo-controlled, CV outcomes study in men with a history of CV disease or multiple CV risk factors. In TRAVERSE, topical testosterone gel increased mean systolic blood pressure by 1.0 mm Hg from baseline to 36 months, whereas a mean decrease from baseline of 0.5 mm Hg was observed in the placebo group at this timepoint, for a mean between-group difference of 1.5 mm Hg. However, the incidences of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction [MI] and non-fatal stroke, were similar between treatment groups (7% for topical testosterone gel vs 7.3% for placebo) *[See Adverse Reactions (6.1)]*.

Monitor blood pressure periodically in men using TESTIM, especially men with hypertension. TESTIM is not recommended for use in patients with uncontrolled hypertension.

5.6 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions *[see Drug Abuse and Dependence (9)]*.

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

5.7 Not for Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, TESTIM is not indicated for use in women *[see Contraindications (4) and Use in Specific Populations (8.1, 8.2)]*.

5.8 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including TESTIM, 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.

5.9 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. TESTIM is not known to cause 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 TESTIM while the cause is evaluated.

5.10 Edema

Androgens, including TESTIM, 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.

5.11 Gynecomastia

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

5.12 Sleep Apnea

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

5.13 Lipid Changes

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

5.14 Hypercalcemia

Androgens, including TESTIM, 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.

5.15 Decreased Thyroxine-binding Globulin

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

5.16 Flammability

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

6 ADVERSE REACTIONS

6.1 Clinical Studies 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 TESTIM 50 mg or 100 mg or placebo gel for up to 90 days. Two hundred five (205) patients received TESTIM 50 mg or 100 mg daily and 99 patients received placebo. Subjects could be counted in both TESTIM 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 TESTIM patients and greater than placebo are listed in Table 1.

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

Event	TESTIM 50 mg (n=103)	TESTIM 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%

Event	TESTIM 50 mg (n=103)	TESTIM 100 mg (n=149)	Placebo (n=99)
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 TESTIM 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 TESTIM, 6 patients had adverse reactions that led to their discontinuation. These events included: depression with suicidal ideation, urinary tract infection, mood swings and hypertension. No TESTIM patients discontinued due to skin reaction. In one foreign Phase 3 trial, one subject discontinued due to a skin-related adverse reaction.

In the pivotal US 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 US and European open-label extension studies, approximately 140 patients received TESTIM for at least 6 months. The results from these studies are consistent with those reported for the US controlled clinical trial.

Blood Pressure Increases

In a 4-month clinical study, 24-hour ambulatory blood pressure monitoring (ABPM) was conducted on 225 patients. ABPM was conducted at baseline and at Week 16 of TESTIM therapy. A total of 113 patients had acceptable ABPM recordings at both baseline and Week 16 and were at least 85% compliant with study drug. In that group, the mean change in 24-hour systolic blood pressure (BP) and diastolic BP from baseline to end-of-treatment at Week 16 (n=113) was 2.7 mm Hg (95% CI 0.7, 4.8) and 1.1 mm Hg (95% CI -0.1, 2.3), respectively. In patients with a history of hypertension who were receiving antihypertensive therapy, the mean ABPM systolic and diastolic BP increased by 1.9 mm Hg [95% CI -1.4, 5.2] and 0.3 mm Hg [95% CI -1.6, 2.2], respectively [n=55]). In patients with no history of hypertension, the mean systolic and diastolic blood pressure increased by 2.2 mm Hg [95% CI -0.4, 4.9] and 1.1 mm Hg [95% CI -0.4, 2.7], respectively [n=56].

3 patients (2.7%) on TESTIM, all of whom were receiving antihypertensive medications at baseline, either started new antihypertensive medications (n=3) or had their antihypertensive medication regimen adjusted (n=0) during the ABPM study.

Of the 225 patients in the ABPM study who used TESTIM, 6 patients (2.7%) were reported to have either an adverse reaction of hypertension (6 patients, 2.7%) or increased blood pressure (0 patients, 0.0%).

Cardiovascular Outcomes

TRAVERSE was a randomized, double-blind, cardiovascular outcomes study to assess the cardiovascular (CV) safety of topical testosterone gel compared to placebo in 5198 hypogonadal men aged 45 to 80 years with a history of CV disease or with multiple CV risk factors. The primary outcome was the incidence of the composite endpoint of major adverse cardiovascular events (MACE), consisting of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke.

The mean duration of therapy was approximately 22 months. The mean duration of follow-up was 33 months. Approximately 61% of all patients discontinued topical testosterone gel or placebo therapy.

The mean patient age (±SD) was 63.3 (7.9) years, with 2452 patients aged 65 years or more (47%); 2847 (about 55%) patients had pre-existing cardiovascular disease, whereas 2357 patients (about 45%) had an elevated cardiovascular risk at baseline, and mean BMI was 35kg/m^2. Approximately 80% of patients were White, 17% were Black, and 3% were of other races or ethnic groups. Approximately 69%, 84%, and 93% had diabetes mellitus, hyperlipidemia, and hypertension, respectively.

The mean serum testosterone concentration at baseline in patients receiving topical testosterone gel was 220.4 ng/dL (n=2596). The mean serum testosterone concentrations at 12 months, 24 months, 36 months, and 48 months in patients receiving topical testosterone gel were 440.5 ng/dL (n=1683), 420.9 ng/dl (n=1125), 428.7 ng/dL (n=731), and 365.2 ng/dL (n=220), respectively.

For patients treated with topical testosterone gel, the incidence of MACE was 7.0% (n=182 events) and for those receiving placebo, the incidence of MACE was 7.3% (n=190 events). The study demonstrated non-inferiority of topical testosterone gel versus placebo because the upper bound of 95% CI was less than the pre-specified risk margin, of 1.5 for MACE (Hazard Ratio 0.96 [95% CI: 0.78, 1.17]).

Additional Adverse Reactions Reported in TRAVERSE

Additional adverse reactions reported in TRAVERSE at an incidence rate >2% in either treatment group and greater in topical testosterone gel versus placebo included: nonfatal arrythmias warranting intervention (5.2% vs 3.3%), atrial fibrillation (3.5% vs 2.4%), acute kidney injury (2.3% vs 1.5%) and bone fracture (3.5% vs 2.5%). For the adverse reaction of bone fracture, each event was adjudicated by clinical review.

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 fabric, such as towels and sheets *[see Warnings and Precautions (5.1)]*.

Vascular Disorders

Venous thromboembolism *[see Warnings and Precautions (5.3)]*

Cardiovascular Disorders

Myocardial infarction, stroke *[see Warnings and Precautions (5.5)]*

Blood and Lymphatic Disorders

Polycythemia *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may 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

Risk Summary

TESTIM is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm based on data from animal studies and its mechanism of action *[see Contraindications (4)*

and Clinical Pharmacology (12.1)]. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal development studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

In developmental studies conducted in rats, rabbits, pigs, sheep, and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased anogenital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant female rats and their offspring exposed to doses approximately twice those used for testosterone replacement therapy.

8.2 Lactation

Risk Summary

TESTIM is not indicated for use in females.

8.3 Females and Males of Reproductive Potential

Infertility

During treatment with large doses of exogenous androgens, including TESTIM, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see Warnings and Precautions (5.8)]*, possible leading to adverse effects on semen parameters including sperm count. Reduced fertility is observed in some men taking testosterone replacement therapy. Testicular atrophy, subfertility, and infertility have also been reported in men who abuse anabolic androgenic steroids *[see Drug Abuse and Dependence (9.2)]*. With either type of use, the impact on fertility may be irreversible.

8.4 Pediatric Use

The safety and effectiveness of TESTIM 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 (5.4)]*.

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

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

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse of men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility, and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

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

10 OVERDOSAGE

There were no reports of overdose in the TESTIM 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 TESTIM, washing the application site with soap and water, and appropriate symptomatic and supportive care.

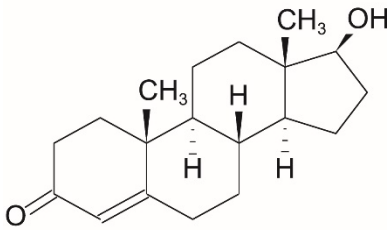
11 DESCRIPTION

TESTIM (testosterone gel) is a clear to translucent hydroalcoholic topical gel containing testosterone, an androgen. TESTIM 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.

One 5-g or two 5-g tubes of TESTIM contains 50 mg or 100 mg of testosterone, respectively, to be applied daily to the skin’s surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period.

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

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



Testosterone

Testim may have an alcoholic/musk odor. Inactive ingredients in TESTIM are purified water, pentadecalactone, carbopol, acrylates, propylene glycol, glycerin, polyethylene glycol, ethanol (74%), 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 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. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has 2 main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, while secondary hypogonadism (hypogonadotropic 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 TESTIM.

12.3 Pharmacokinetics

Absorption

TESTIM (testosterone gel) delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (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

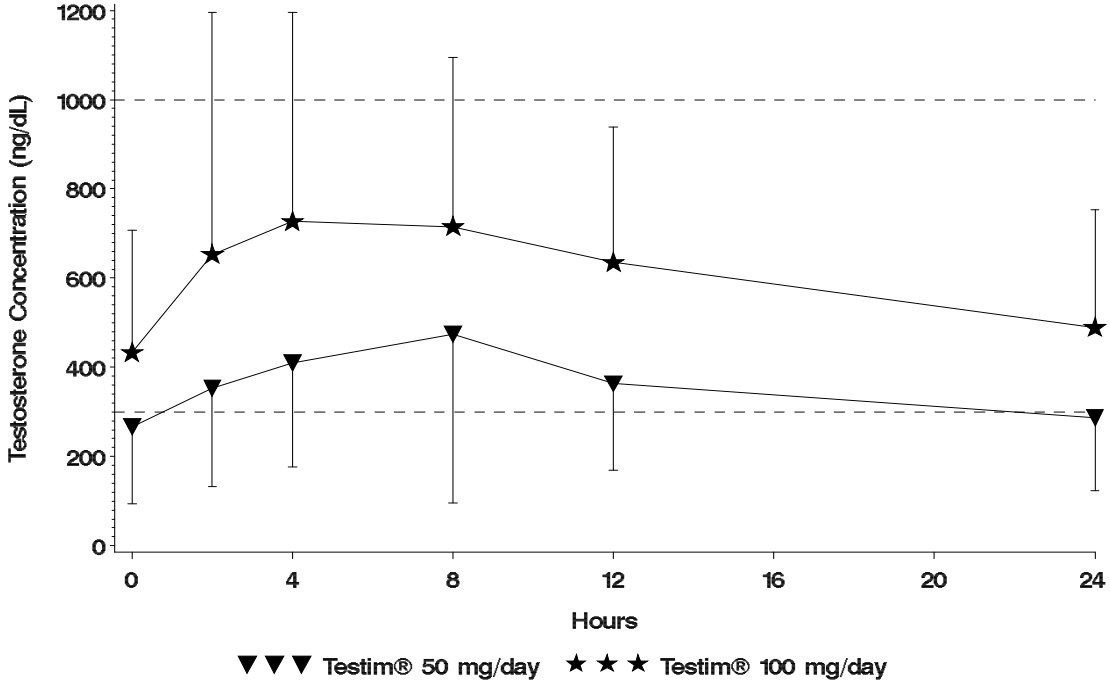
In single-dose studies, when either TESTIM 50 mg or 100 mg was administered, absorption of testosterone into the blood continued for the entire 24-hour dosing period. Also, mean peak and average serum concentrations within the normal range were achieved within 24 hours.

Multiple Dose

With single daily applications of TESTIM 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 TESTIM 50 mg or TESTIM 100 mg for 30 days.

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



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

Distribution

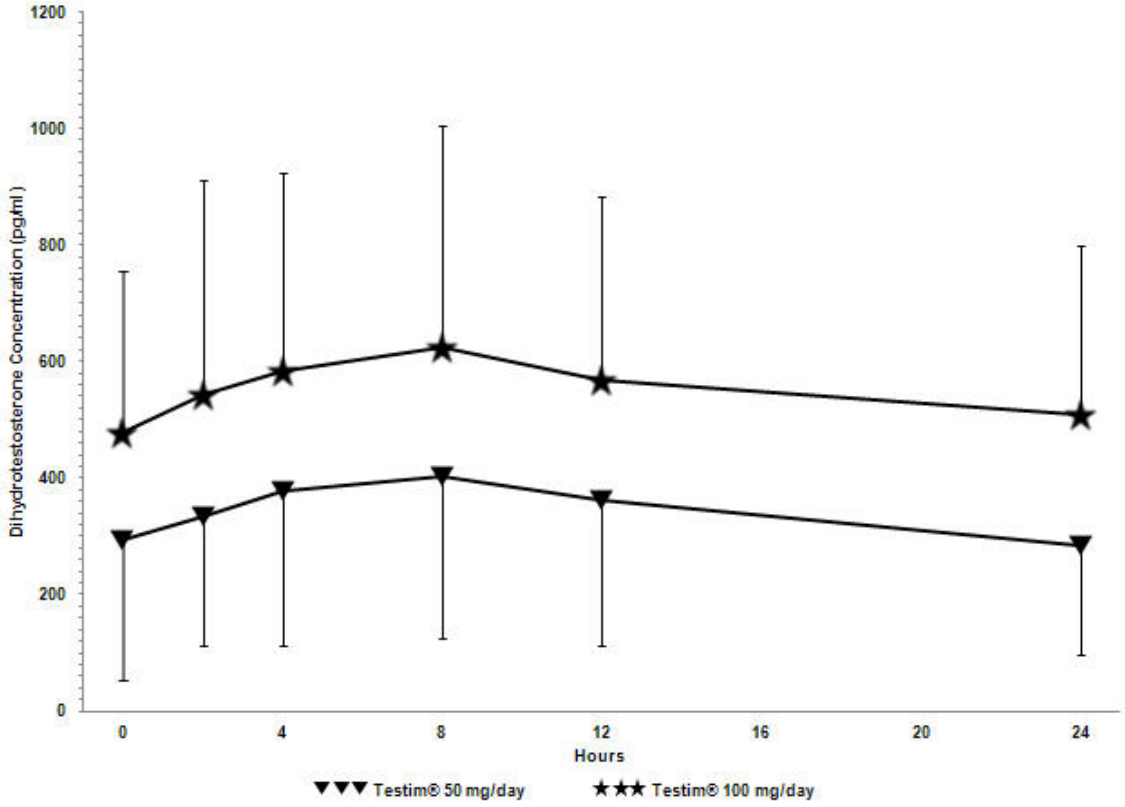
Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins.

Metabolism

Testosterone is metabolized to various 17-keto steroids through 2 different pathways. The major active metabolites of testosterone are estradiol and DHT. The average daily DHT concentration produced by TESTIM 100 mg at Day 30 was 555 (± 293) pg/mL and by TESTIM 50 mg at Day 30 was 346 (± 212) pg/mL.

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

Figure 2: Mean Steady-State Serum Dihydrotestosterone (± SD) (pg/mL) Concentrations on Day 30 in Patients Applying TESTIM 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 Testosterone Transfer from Male Patients to Female Partners

The potential for dermal testosterone transfer following TESTIM use was evaluated in two clinical trials with males dosed with TESTIM and their untreated female partners.

In the first trial, 30 couples were evenly randomized to 5 groups. In the first 4 groups, 100 mg of TESTIM was applied to the male abdomen and the couples were then asked to rub abdomen-to-

abdomen for 15 minutes at 1 hour, 4 hours, 8 hours, or 12 hours after dose application, respectively. In these couples, serum testosterone concentrations in female partners increased from baseline by at least 6 times and potential for transfer was seen at all time points.

When 6 males used a shirt to cover the abdomen at 15 minutes post-application and partners again rubbed abdomens for 15 minutes at the 1-hour time point, serum testosterone concentrations in female partners increased from baseline by approximately 3 times.

In the second trial, 24 couples were evenly randomized to 4 groups. TESTIM 100 mg was applied to the male upper arms and shoulders. In one group, 15 minutes of direct skin-to-skin rubbing began at 4 hours after application. In these 6 women, all of whom showered immediately after the rubbing activity, mean maximum serum testosterone concentrations increased from baseline by approximately 4 times. When males wore a long-sleeved T-shirt and rubbing was started at 1 and at 4 hours after application, the transfer of testosterone from male to female partners was prevented.

Effect of Showering

The effect of showering (with mild soap) at 1, 2, and 6 hours post application of TESTIM 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 2 or more hours post drug application, serum testosterone concentrations remained within the normal range.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog, and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Hypogonadal Males

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

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

Table 2 summarizes the mean testosterone concentrations on Day 30 for patients receiving TESTIM 50 mg or 100 mg.

Table 2: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30

	TESTIM 50 mg (n=94)	**TESTIM 100 mg (n=95)**	**Placebo (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

TESTIM is supplied in unit-dose tubes in cartons of 30. Each tube contains 50 mg testosterone in 5 g of gel, and is supplied as follows:

NDC Number	**Package Size**
66887-001-05	30 tubes: 50 mg testosterone in 5 g of gel per tube

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].

Discard used TESTIM tubes in household trash in a manner that prevents accidental exposure of women, children, or pets *[see Boxed Warning and Warnings and Precautions (5.1)]*. Contents are flammable *[see Warnings and Precautions (5.16)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

17.1 Men with Known or Suspected Carcinoma of the Breast or Prostate

Men with known or suspected prostate or breast cancer should not use TESTIM *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

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

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

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

- In children; unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior
- In women; changes in hair distribution, increase in acne, or other signs of testosterone effects
- The possibility of secondary exposure to TESTIM should be brought to the attention of a healthcare provider
- TESTIM 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 TESTIM in men *[see Medication Guide]*:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using TESTIM.
- Patients using TESTIM 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 TESTIM 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 (5.1), and Clinical Pharmacology (12.3)]*.

17.3 Potential Adverse Reactions with Androgens

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

- Changes in urinary habits, such as increased urination at night, trouble starting 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
- Venous thromboembolism, the signs and symptoms of which may include lower limb pain, edema, or erythema; dyspnea; or chest pain.
- Increased blood pressure that can increase cardiovascular risk over time.

17.4 Patients Should Be Advised of the Following Instructions for Use

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

Manufactured for:
Endo USA
Malvern, PA 19355

Manufactured by:
DPT Laboratories, Ltd.
San Antonio, TX 78215

or

Contract Pharmaceuticals Limited
Mississauga, ON, Canada L5N 6R8

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