Testosterone Gel
HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Testosterone gel for topical use **CIII**

Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

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

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

Warnings and Precautions (5.6) 12/2016

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

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

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

Limitations of use:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION and FDA approved Medication Guide

Revised: 07/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

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

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

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

Limitations of use:

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

2 DOSAGE AND ADMINISTRATION

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

2.1 Dosing and Dose Adjustment

The recommended starting dose of testosterone gel is 40 mg of testosterone (4 pump

5.2 Potential for Secondary Exposure to Testosterone

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

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

5.3 Polycythemia

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

5.4 Venous Thromboembolism

There have been Postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as testosterone gel. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with testosterone gel and initiate appropriate workup and management.

5.5 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal

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

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

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

9 DRUG ABUSE AND DEPENDENCE

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

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

Abuse-Related Adverse Reactions
Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.
The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.
The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.
The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty. Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence
Behaviors Associated with Addiction
Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, implant induced cervical-uterine tumors metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

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

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

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

Dose titrations on Days 14, 35 and 60 resulted in mean (SD) C_{avg} and C_{max} for final doses of 10 mg - 70 mg on Day 90 shown in Table 5.

Table 5 Mean (±SD) Steady-State Testosterone Concentrations (C_{avg} and C_{max}) by final dose on Day 90

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

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

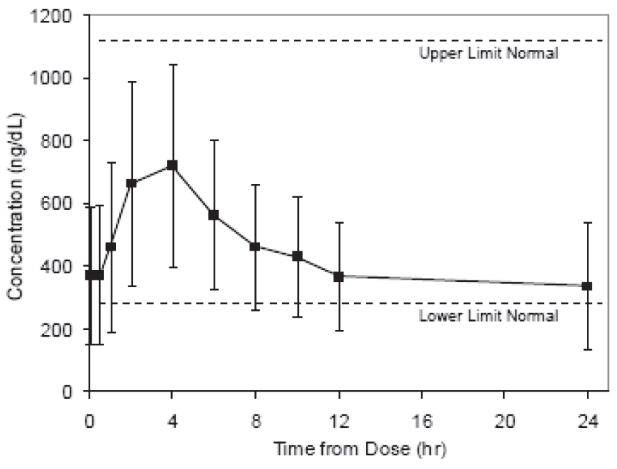

Figure 2 Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 90 (N=129)

Additionally, there were no clinically significant changes from baseline for sex hormone