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Product Name: Testosterone Gel 1% Outsert

Part #: OS418-01-1-04

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Color Information

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Front - Black	Perf. Line		
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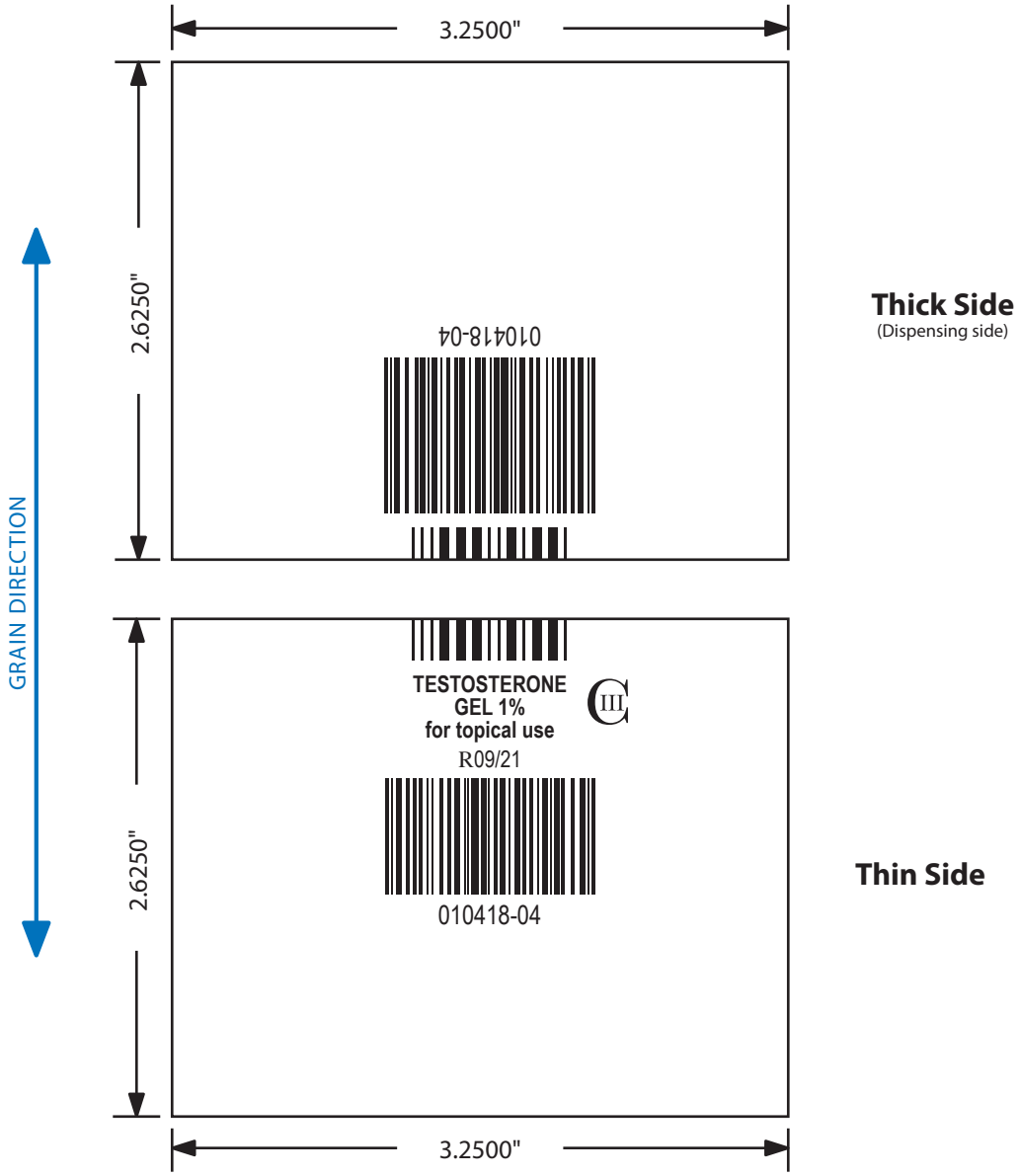
Rev: 4

Rev.#	Date	BC Grade	Artist
1	01/12/22	A	TA/KH
2	01/20/22	A	TA/MS
3	01/21/22	A	MS
4	01/25/22	A	MS

Glues



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27.5000"

16.5000"

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TESTOSTERONE GEL 1% safely and effectively. See full prescribing information for TESTOSTERONE GEL 1%.

Testosterone Gel 1%, for topical use
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 1% is 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 1% in men with "age-related hypogonadism" have not been established. **(1)**
- Safety and efficacy of Testosterone Gel 1% 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

- **Dosage and Administration for Testosterone Gel 1% differs from Testosterone Gel 1.62 %. For dosage and administration of Testosterone Gel 1.62% refer to its full prescribing information. (2)**
- Prior to initiating Testosterone Gel 1%, 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 1% is 50 mg of testosterone (two 25 mg packets, or one 50 mg packet), applied once daily in the morning. **(2.1)**
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply Testosterone Gel 1% to any other parts of the body including the genitals, chest, armpits (axillae), knees, or back. **(2.2)**
- Dose adjustment: Testosterone Gel 1% can be dose adjusted using 50 mg, 75 mg, or 100 mg of testosterone on the basis of total serum testosterone concentration. The dose should be titrated based on the serum testosterone concentration. Additionally, serum testosterone concentration should be assessed periodically. **(2.1)**
- Patients should wash hands immediately with soap and water after applying Testosterone Gel 1% and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. **(2.2)**

DOSAGE FORMS AND STRENGTHS

Testosterone Gel 1% for topical use is available as follows:
- Packets containing 25 mg of testosterone. **(3)**
- Packets containing 50 mg of testosterone. **(3)**

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected prostate cancer. **(4, 5.1)**
- Women who are pregnant. Testosterone may cause fetal harm. **(4, 8.1)**

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 1%. Secondary exposure to testosterone can produce signs of virilization. Testosterone Gel 1% 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 preexisting cardiac, renal, or hepatic disease. **(5.10, 6.2)**
- 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 1% is flammable until dry. **(5.16)**

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1-877-244-9825 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 INR and prothrombin time is recommended. **(7.2)**
- Use of testosterone with adrenocorticotrophic 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 1% to assess the potential risks of cardiovascular disease and prostate cancer. **(8.5)**

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2021

TESTOSTERONE GEL 1% for topical use
R09/21

010418-04

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 1% is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:
- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], 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 Testosterone Gel 1% in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- Safety and efficacy of Testosterone Gel 1% in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure (1, 12.3).

2 DOSAGE AND ADMINISTRATION

Dosage and Administration for Testosterone Gel 1% differs from Testosterone Gel 1.62%. For dosage and administration of Testosterone Gel 1.62% refer to its full prescribing information. (2)

Prior to initiating Testosterone Gel 1%, 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 1% is 50 mg of testosterone (two 25 mg packets, or one 50 mg packet), applied topically once daily in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day).

Dose Adjustment

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

The application site and dose of Testosterone Gel 1% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

Testosterone Gel 1% should be applied to clean, dry, healthy, intact skin of the right and left upper arms/shoulders and/or right and left abdomen. Area of application should be limited to the area that will be covered by the patient's short sleeve T-shirt. Do not apply Testosterone Gel 1% to any other part of the body including the genitals, chest, armpits (axillae), knees, or back. Testosterone Gel 1% should be evenly distributed between the right and left upper arms/shoulders or both sides of the abdomen.

The prescribed daily dose of Testosterone Gel 1% should be applied to the right and left upper arms/shoulders and/or right/left abdomen as shown in the shaded areas in the figure below.

After applying the gel, the application site should be allowed to dry prior to dressing. Hands should be washed thoroughly with soap and water after application. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including Testosterone Gel 1%, are flammable.

The patient should be advised to avoid swimming or showering for at least 5 hours after the application of Testosterone Gel 1%.

Packets

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

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from Testosterone Gel 1%-treated skin:
- Children and women should avoid contact with unwashed or unclothed application site(s) of men using Testosterone Gel 1%.
- Patients should wash hands with soap and water immediately after application of Testosterone Gel 1%.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the gel has dried.
- Prior to situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which Testosterone Gel 1% 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 1% for topical use is available as follows:
- A unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel.
- A unit dose packet containing 50 mg of testosterone provided in 5 g of gel.

4 CONTRAINDICATIONS

- Testosterone Gel 1% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Nonclinical Toxicology (13.1)]*.
- Testosterone Gel 1% is contraindicated in women who are pregnant. Testosterone Gel 1% can cause virilization of the female fetus when administered to a pregnant woman. Pregnant women need to be aware of the potential for transfer of testosterone from men treated with Testosterone Gel 1%. If a pregnant woman is exposed to Testosterone Gel 1%, she should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

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

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4), Adverse Reactions (6.1) and Nonclinical Toxicology (13.1)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using Testosterone Gel 1% *[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 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 Testosterone Gel 1% and initiate appropriate workup and management *[see Adverse Reactions (6.2)]*.

5.5 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men.

Patients should be informed of this possible risk when deciding whether to use or to continue to use Testosterone Gel 1%.

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 Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, Testosterone Gel 1% 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 Testosterone Gel 1%, 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 has produced multiple hepatic adenomas. Testosterone Gel 1% is not known to cause these adverse effects.

5.10 Edema

Androgens, including Testosterone Gel 1%, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease *[see Adverse Reactions (6.2)]*.

5.11 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including Testosterone Gel 1%, for hypogonadism.

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 *[see Adverse Reactions (6.2)]*.

5.13 Lipids

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

5.14 Hypercalcemia

Androgens, including Testosterone Gel 1%, 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 Testosterone Gel 1%, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.16 Flammability

Alcohol based products, including Testosterone Gel 1%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the Testosterone Gel 1% has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Hypogonadal Men

Table 1 shows the incidence of all adverse events judged by the investigator to be at least possibly related to treatment with Testosterone Gel 1% and reported by >1% of patients in a 180 Day, Phase 3 study.

Table 1: Adverse Events Possibly, Probably or Definitely Related to Use of Testosterone Gel 1% in the 180-Day Controlled Clinical Trial

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

* *Lab test abnormal* occurred in nine patients with one or more of the following events reported: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalaemia, decreased HDL, elevated glucose, elevated creatinine, elevated total bilirubin.

** *Prostate disorders* included five patients with enlarged prostate, one with BPH, and one with elevated PSA results.

*** *Testis disorders* were reported in two patients: one with left varicocele and one with slight sensitivity of left testis.

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

In this 180 day clinical trial, skin reactions at the site of application were reported with Testosterone Gel 1%, but none was severe enough to require treatment or discontinuation of drug.

Six patients (4%) in this trial had adverse events that led to discontinuation of Testosterone Gel 1%. These events included: cerebral hemorrhage, convulsion (neither of which were considered related to Testosterone Gel 1% administration), depression, sadness, memory loss, elevated prostate specific antigen, and hypertension. No Testosterone Gel 1% patient discontinued due to skin reactions.

In a separate uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with Testosterone Gel 1%; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other.

In a 3 year, flexible dose, extension study, the incidence of all adverse events judged by the investigator to be at least possibly related to treatment with Testosterone Gel 1% and reported by > 1% of patients is shown in **Table 2**.

Table 2: Adverse Events Possibly, Probably or Definitely Related to Use of Testosterone Gel 1% in the 3 Year, Flexible Dose, Extension Study

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

* *Lab test abnormal* occurred in 15 patients with one or more of the following events reported: elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, elevated HDL, elevated serum creatinine.

* *Urinary symptoms* included nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream.

** *Testis disorders* included three patients. There were two with a non-palpable testis and one with slight testicular tenderness.

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

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

Increases in Serum PSA Observed in Clinical Trials of Hypogonadal Men

During the initial 6-month study, the mean change in PSA values had a statistically significant increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter in the 162 hypogonadal men on Testosterone Gel 1% in the 3-year extension study. There was no additional statistically significant increase observed in mean PSA from 6 months through 36 months. However, there were increases in serum PSA observed in approximately 18% of individual patients. The overall mean change from baseline in serum PSA values for the entire group from month 6 to 36 was 0.11 ng/mL.

Twenty-nine patients (18%) met the per-protocol criterion for increase in serum PSA, defined as >2X the baseline or any single serum PSA >4 ng/mL. Most of these (25/29) met this criterion by at least doubling of their PSA from baseline. In most cases where PSA at least doubled (22/25), the maximum serum PSA value was still <2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%).

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Testosterone Gel 1%. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (**Table 3**).

Table 3: Adverse Drug Reactions from Postmarketing Experience of Testosterone Gel 1% by MedDRA System Organ Class

Blood and the lymphatic system disorders:	Elevated Hgb, Hct (polycythemia)
Cardiovascular disorders:	Myocardial infarction, stroke
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders and administration site reactions:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination
Hepatobiliary disorders:	Abnormal liver function tests (e.g. transaminases, elevated GGTP, bilirubin)
Investigations:	Elevated PSA, electrolyte changes (nitrogen, calcium, potassium, phosphorus, sodium), changes in serum lipids (hyperlipidemia, elevated triglycerides, decreased HDL), impaired glucose tolerance, fluctuating testosterone concentrations, weight increase
Neoplasms benign, malignant and unspecified (cysts and polyps):	Prostate cancer
Nervous system:	Headache, dizziness, sleep apnea, insomnia
Psychiatric disorders:	Depression, emotional lability, decreased libido, nervousness, hostility, amnesia, anxiety
Reproductive system and breast disorders:	Gynecomastia, mastodynia, prostatic enlargement, testicular atrophy, oligospermia, priapism (frequent or prolonged erections)
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (pruritus, dry skin, erythema, rash, discolored hair, paresthesia), sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes), venous thromboembolism

Secondary Exposure to Testosterone in Children

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

7 DRUG INTERACTIONS

7.1 Insulin

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

7.2 Oral Anticoagulants

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

7.3 Corticosteroids

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Testosterone Gel 1% is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm when administered to a pregnant woman 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 developmental 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

MEDICATION GUIDE
TESTOSTERONE GEL 1%
(tes-TOS-te-rōn) for topical use

What is the most important information I should know about Testosterone Gel 1%?

1. Testosterone Gel 1% can transfer from your body to others including children and women. Children and women should avoid contact with the unwashed or not covered (unclothed) areas where Testosterone Gel 1% has been applied to your skin. Early signs and symptoms of puberty have occurred in young children who have come in direct contact with Testosterone by touching areas where men have used Testosterone Gel 1%.

Children

Signs and symptoms of early puberty in a child when they come in direct contact with Testosterone Gel 1% may include:

Abnormal sexual changes:
- enlarged penis or clitoris.
- early growth of hair near the vagina or around the penis (pubic hair).
- erections or acting out sexual urges (sex drive).

Behavior problems:
- acting aggressively, behaving in an angry or violent way.

Women

Signs and symptoms in women when they come in direct contact with Testosterone Gel 1% may include:
- changes in body hair.
- an abnormal increase in pimples (acne).

Stop using Testosterone Gel 1% and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have happened through accidental touching of the area where you have applied Testosterone Gel 1%.

2. To lower the risk of transfer of Testosterone Gel 1% from your body to others, follow these important instructions:
- Apply Testosterone Gel 1% only to areas of your shoulders, upper arms, or stomach area (abdomen) that will be covered by a short sleeve t-shirt.
- Wash your hands right away with soap and water after applying Testosterone Gel 1%.
- After the gel has dried, cover the application area with clothing. Keep the area covered until you have washed the gel off 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 child or woman touches the area where you have applied Testosterone Gel 1%, that area on the child or woman should be washed well with soap and water right away.

What is Testosterone Gel 1%?

Testosterone Gel 1% is a prescription medicine that contains testosterone. Testosterone Gel 1% is used to treat adult males who have low or no testosterone due to certain medical conditions.

Improper use of Testosterone Gel 1% may affect bone growth in children.

Testosterone Gel 1% is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your Testosterone Gel 1% in a safe place to protect it. Never give your Testosterone Gel 1% to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

Testosterone Gel 1% is not meant for use in women.

Do not use Testosterone Gel 1% if you:
- have breast cancer.
- have or might have prostate cancer.
- are pregnant. Testosterone Gel 1% may harm your unborn baby.
- Women who are pregnant should avoid contact with the area of skin where Testosterone Gel 1% has been applied.

Before using Testosterone Gel 1%, tell your healthcare provider about all of your medical conditions, including 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).

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using Testosterone Gel 1% with certain other medicines can affect each other.

Especially tell your healthcare provider if you take:
- insulin
- corticosteroids
- medicines that decrease blood clotting (blood thinners)

How should I use Testosterone Gel 1%?
- See the detailed **Instructions for Use** for information about how to use Testosterone Gel 1% at the end of this Medication Guide.
- It is important that you apply Testosterone Gel 1% exactly as your healthcare provider tells you to.
- Your healthcare provider may change your Testosterone Gel 1% dose. **Do not** change your Testosterone Gel 1% dose without talking to your healthcare provider.
- Apply Testosterone Gel 1% at the same time each morning. Testosterone Gel 1% should be applied after showering or bathing.

What are the possible side effects of Testosterone Gel 1%?

Testosterone Gel 1% can cause serious side effects including:

See **"What is the most important information I should know about Testosterone Gel 1%?"**
- **If you already an enlarged prostate, your symptoms can get worse while using Testosterone Gel 1%.** This can include:
- increased urination at night.
- trouble starting your urine stream.
- having to pass urine many times during the day.
- having an urge 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 any other prostate problems before you start and while you use Testosterone Gel 1%.

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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 ano-genital 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

Testosterone Gel 1% is not indicated for use in women.

8.3 Females and Males of Reproductive Potential

Infertility

Testis disorder, testicular atrophy, and oligospermia have been identified during use of Testosterone Gel 1% *[see Adverse Reactions (6.1, 6.2)]*.

During treatment with large doses of exogenous androgens, including Testosterone Gel 1%, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see Warnings and Precautions (5.8)]*. 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 efficacy of Testosterone Gel 1% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing Testosterone Gel 1% to determine whether efficacy in those over 65 years of age differs from younger subjects. Additionally, there is insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer.

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

8.6 Renal Impairment

No studies were conducted 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 1% 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 by 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 is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone concentrations of up to 11,400 ng/dL with a cerebrovascular accident.

Treatment of overdosage would consist of discontinuation of Testosterone Gel 1%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

11 DESCRIPTION

Testosterone Gel 1% is a clear, colorless hydroalcoholic gel containing testosterone.

The active pharmacologic ingredient in Testosterone Gel 1% is testosterone, an androgen. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:

Testosterone

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

Pharmacologically inactive ingredients in Testosterone Gel 1% are carbomer 940, ethanol 68.9%, isopropyl myristate, purified water, and sodium hydroxide. These ingredients are not pharmacologically active.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, 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 1%.

12.3 Pharmacokinetics

Absorption

Testosterone Gel 1% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (298 to 1043 ng/dL) seen in healthy men. Testosterone Gel 1% provides continuous transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

Testosterone Gel 1% is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from Testosterone Gel is absorbed into systemic circulation. In a study with Testosterone Gel 1% 100 mg, all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady-state concentration by the end of the first 24 hours and are at steady state by the second or third day of dosing.

With single daily applications of Testosterone Gel 1%, follow-up measurements 30, 90 and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. **Figure 1** summarizes the 24-hour pharmacokinetic profiles of testosterone for hypogonadal men (less than 300 ng/dL) maintained on Testosterone Gel 1% 50 mg or 100 mg for 30 days. The average (± SD) daily testosterone concentration produced by Testosterone Gel 1% 100 mg on Day 30 was 792 (± 294) ng/dL and by Testosterone Gel 1% 50 mg 566 (± 262) ng/dL.

Figure 1: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying Testosterone Gel 1% Once Daily

Distribution

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

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT).

DHT concentrations increased in parallel with testosterone concentrations during Testosterone Gel 1% treatment. The mean steady-state DHT/T ratio during 180 days of Testosterone Gel treatment ranged from 0.23 to 0.29 (50 mg of Testosterone Gel 1%/day) and from 0.27 to 0.33 (100 mg of Testosterone Gel 1%/day).

Excretion

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

The potential for dermal testosterone transfer following Testosterone Gel 1% use was evaluated in a clinical study between males dosed with Testosterone Gel 1% and their untreated female partners. Two (2) to 12 hours after application of 100 mg of testosterone administered as Testosterone Gel 1% by the male subjects, the couples (N = 38 couples) engaged in daily, 15-minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the Testosterone Gel 1% application sites. Under these study conditions, all unprotected female partners had a serum testosterone concentration >2 times the baseline value at some time during the study. When a shirt covered the application site(s), the transfer of testosterone from the males to the female partners was completely prevented.

Testosterone Transfer from Male Patients to Female Partners

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 to the lungs. 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 rats, dogs, and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Hypogonadal Males

Testosterone Gel 1% was evaluated in a multi-center, randomized, parallel-group, active-controlled, 180-day trial in 227 hypogonadal men. The study was conducted in 2 phases. During the Initial Treatment Period (Days 1-90), 73 patients were randomized to Testosterone Gel 1% 50 mg daily, 78 patients to Testosterone Gel 1% 100 mg daily, and 76 patients to a non-scrotal testosterone transdermal system. The study was double-blind for dose of Testosterone Gel 1% but open-label for active control. Patients who were originally randomized to Testosterone Gel 1% and who had single-sample serum testosterone concentrations above or below the normal range on Day 60 were titrated to 75 mg daily on Day 91. During the Extended Treatment Period (Days 91-180), 51 patients continued on Testosterone Gel 1% 50 mg daily, 52 patients continued on Testosterone Gel 1% 100 mg daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received Testosterone Gel 1% 75 mg daily. Upon completion of the initial study, 163 enrolled and 162 patients received treatment in an open-label extension study of Testosterone Gel 1% for an additional period of up to 3 years.

Mean peak, trough and average serum testosterone concentrations within the normal range (298-1043 ng/dL) were achieved on the first day of treatment with doses of 50 mg and 100 mg of Testosterone Gel 1%. In patients continuing on Testosterone Gel 1% 50 mg and 100 mg, these mean testosterone concentrations were maintained within the normal range for the 180-day duration of the original study. **Figure 2** summarizes the 24-hour pharmacokinetic profiles of testosterone administered as Testosterone Gel 1% for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed Testosterone Gel 1% treatment.

Figure 2: Mean Steady-State Testosterone Concentrations in Patients with Once-Daily Testosterone Gel 1% Therapy

Table 4 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 50 mg, 75 mg, or 100 mg of Testosterone Gel 1%. The 75 mg dose produced mean concentrations intermediate to those produced by 50 mg and 100 mg of Testosterone Gel 1%.

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

	50 mg	75 mg	100 mg
	N = 44	N = 37	N = 48
C_{avg}	555 ± 225	601 ± 309	713 ± 209
C_{max}	830 ± 347	901 ± 471	1083 ± 434
C_{min}	371 ± 165	406 ± 220	485 ± 156

Of 129 hypogonadal men who were appropriately titrated with Testosterone Gel 1% and who had sufficient data for analysis, 87% achieved an average serum testosterone concentration within the normal range on Treatment Day 180.

In patients treated with Testosterone Gel 1%, there were no observed differences in the average daily serum testosterone concentrations at steady-state based on age, cause of hypogonadism, or body mass index.

DHT concentrations increased in parallel with testosterone concentrations at Testosterone Gel 1% doses of 50 mg/day and 100 mg/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with Testosterone Gel 1% 50 or 100 mg/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of SHBG decreased very slightly (1 to 11%) during Testosterone Gel 1% treatment. In men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and time-dependent manner during treatment with Testosterone Gel 1%.

14.2 Phototoxicity in Humans

The photoxic potential of Testosterone Gel 1% was evaluated in a double-blind, single-dose study in 27 subjects with photosensitive skin types. The Minimal Erythema Dose (MED) of ultraviolet radiation was determined for each subject. A single 24 (+1) hour application of duplicate patches containing test articles (placebo gel, Testosterone Gel, or saline) was made to naive skin sites on Day 1. On Day 2, each subject received five exposure times of ultraviolet radiation, each exposure being 25% greater than the previous one. Skin evaluations were made on Days 2 to 5. Exposure of test and control article application sites to ultraviolet light did not produce increased inflammation relative to non-irradiated sites, indicating no phototoxic effect.

16 HOW SUPPLIED/STORAGE AND HANDLING

Testosterone Gel 1% is supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

NDC 64380-151-02 30 packets (a unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel)
NDC 64380-152-02 30 packets (a unit dose packet containing 50 mg of testosterone provided in 5 g of gel)

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Disposal

Used Testosterone Gel 1% packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

Patients should be informed of the following:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use Testosterone Gel 1% *[see Contraindications (4) and Warnings and Precautions (5.1)]*

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

Secondary exposure to testosterone in children and women can occur with the use of Testosterone Gel in men *[see Warnings and Precautions (5.2)]*. 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 1% 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 1% should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water after application
  - **Cover the application site(s)** with clothing after the gel has dried
  - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated
  - In the event that unwashed or unclothed skin to which Testosterone Gel 1% has been applied comes in contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

17.3 Potential Adverse Reactions with Androgens

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

- Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should Be Advised of the Following Instructions for Use:

- **Read the Medication Guide before starting Testosterone Gel 1% therapy and to reread it each time the prescription is renewed**
- **Testosterone Gel 1% 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 1% out of the reach of children**
- **Testosterone Gel 1% 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 1% is prescribed to meet the patient's specific needs; therefore, the patient should never share Testosterone Gel 1% with anyone.
- Wait 5 hours before swimming or washing following application of Testosterone Gel 1%. This will ensure that the greatest amount of Testosterone Gel 1% is absorbed into their system

MEDICATION GUIDE
TESTOSTERONE GEL 1% ℞
(tes-TOS-te-rōn) for topical use

What is the most important information I should know about Testosterone Gel 1%?

1. Testosterone Gel 1% can transfer from your body to others including, children and women. Children and women should avoid contact with the unwashed or not covered (unclothed) areas where Testosterone Gel 1% has been applied to your skin. Early signs and symptoms of puberty have occurred in young children who have come in direct contact with testosterone by touching areas where men have used Testosterone Gel 1%.

Children

Signs and symptoms of early puberty in a child when they come in direct contact with Testosterone Gel 1% may include:

Abnormal sexual changes:

- enlarged penis or clitoris.
- early growth of hair near the vagina or around the penis (pubic hair).
- erections or acting out sexual urges (sex drive).

Behavior problems:

- acting aggressively, behaving in an angry or violent way.

Women

Signs and symptoms in women when they come in direct contact with Testosterone Gel 1% may include:

- changes in body hair.
- an abnormal increase in pimples (acne).

Stop using Testosterone Gel 1% and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have happened through accidental touching of the area where you have applied Testosterone Gel 1%.

2. To lower the risk of transfer of Testosterone Gel 1% from your body to others, follow these important instructions:

- Apply Testosterone Gel 1% only to areas of your shoulders, upper arms, or stomach area (abdomen) that will be covered by a short sleeve t-shirt.
- Wash your hands right away with soap and water after applying Testosterone Gel 1%.
- After the gel has dried, cover the application area with clothing. Keep the area covered until you have washed the gel off 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 child or woman touches the area where you have applied Testosterone Gel 1%, that area on the child or woman should be washed well with soap and water right away.

What is Testosterone Gel 1%?

Testosterone Gel 1% is a prescription medicine that contains testosterone. Testosterone Gel 1% is used to treat adult males who have low or no testosterone due to certain medical conditions.

- Your healthcare provider will test your blood before you start and while you are using Testosterone Gel 1%.
- It is not known if Testosterone Gel 1% is safe or effective to treat men who have low testosterone due to aging.
- It is not known if Testosterone Gel 1% is safe or effective in children younger than 18 years old. Improper use of Testosterone Gel 1% may affect bone growth in children.

Testosterone Gel 1% is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your Testosterone Gel 1% in a safe place to protect it. Never give your Testosterone Gel 1% to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

Testosterone Gel 1% is not meant for use in women.

Do not use Testosterone Gel 1% if you:

- have breast cancer.
- have or might have prostate cancer.
- are pregnant. Testosterone Gel 1% may harm your unborn baby.
- Women who are pregnant should avoid contact with the area of skin where Testosterone Gel 1% has been applied.

Before using Testosterone Gel 1%, tell your healthcare provider about all of your medical conditions, including 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).

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using Testosterone Gel 1% with certain other medicines can affect each other.

Especially, tell your healthcare provider if you take:

- insulin
- corticosteroids
- medicines that decrease blood clotting (blood thinners)

How should I use Testosterone Gel 1%?

- See the detailed **Instructions for Use** for information about how to use Testosterone Gel 1% at the end of this Medication Guide.
- It is important that you apply Testosterone Gel 1% exactly as your healthcare provider tells you to.
- Your healthcare provider may change your Testosterone Gel 1% dose. **Do not** change your Testosterone Gel 1% dose without talking to your healthcare provider.
- Apply Testosterone Gel 1% at the same time each morning. Testosterone Gel 1% should be applied after showering or bathing.

What are the possible side effects of Testosterone Gel 1%?

Testosterone Gel 1% can cause serious side effects including:

See **"What is the most important information I should know about Testosterone Gel 1%?"**

- **If you already an enlarged prostate, your symptoms can get worse while using Testosterone Gel 1%.** This can include:
  - increased urination at night.
  - trouble starting your urine stream.
  - having to pass urine many times during the day.
  - having an urge 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 1%.
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **Possible increased risk of heart attack or stroke.**
- **In large doses Testosterone Gel 1% may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Have problems breathing while you sleep (sleep apnea).**

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of Testosterone Gel 1% include:

- acne
- skin irritation where Testosterone Gel 1% is applied
- lab test changes
- increased prostate specific antigen (a test used to screen for prostate cancer).

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

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

These are not all the possible side effects of Testosterone Gel 1%. For more information, ask your healthcare provider or pharmacist.

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

General information about the safe and effective use of TESTOSTERONE GEL 1%

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Testosterone Gel 1% for a condition for which it was not prescribed. Do not give Testosterone Gel 1% to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about Testosterone Gel 1% that is written for health professionals.

What are the ingredients in Testosterone Gel 1%?

Active ingredient: Testosterone

Inactive ingredients: Carbomer 940, ethyl alcohol 68.9%, isopropyl myristate, purified water and sodium hydroxide.

For more information call Strides Pharma Inc. at 1-877-244-9825 or visit www.strides.com

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

INSTRUCTIONS FOR USE
TESTOSTERONE GEL 1% ℞
(tes-TOS-te-rōn) for topical use

Read this Instructions for Use for Testosterone Gel 1% before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

Applying Testosterone Gel 1%:

- Before applying Testosterone Gel 1%, make sure that your shoulders, upper arms, or stomach are clean, dry, and there is no broken skin.
- The application sites for Testosterone Gel 1% are the shoulders, upper arms, or stomach area (abdomen) that will be covered by a short sleeve t-shirt (see **Figure A**). **Do not** apply Testosterone Gel 1% to any other parts of your body such as your penis, scrotum, chest, armpits (axillae), knees, or back.

(Figure A)

- Tear open the packet completely at the dotted line. Squeeze from the bottom of the packet to the top.
- Squeeze all of the Testosterone Gel 1% out of the packet into the palm of your hand.
- Apply Testosterone Gel 1% to the application site. You may also apply Testosterone Gel 1% from the packet directly to the application site.
- **Let the application areas dry completely before putting on a t-shirt.**
- **Testosterone Gel 1% is flammable until dry. Let Testosterone Gel 1% dry before smoking or going near an open flame.**
- **Wash your hands with soap and water right away** after applying Testosterone Gel 1%.
- Avoid showering, swimming, or bathing for at least 5 hours after you apply Testosterone Gel 1%.

How should I store Testosterone Gel 1%?

- Store Testosterone Gel 1% at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away used Testosterone Gel 1% in the household trash. Be careful to prevent accidental exposure of children or pets.
- Keep Testosterone Gel 1% away from fire.

Keep Testosterone Gel 1% and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
Strides Pharma Inc.
East Brunswick, NJ 08816

Revised: 09/2021 OS418-01-1-04

- Apply Testosterone Gel 1% to the application site. You may also apply Testosterone Gel 1% from the packet directly to the application site.
- **Let the application areas dry completely before putting on a t-shirt.**
- **Testosterone Gel 1% is flammable until dry. Let Testosterone Gel 1% dry before smoking or going near an open flame.**
- **Wash your hands with soap and water right away** after applying Testosterone Gel 1%.
- Avoid showering, swimming, or bathing for at least 5 hours after you apply Testosterone Gel 1%.

How should I store Testosterone Gel 1%?

- Store Testosterone Gel 1% at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away used Testosterone Gel 1% in the household trash. Be careful to prevent accidental exposure of children or pets.
- Keep Testosterone Gel 1% away from fire.

Keep Testosterone Gel 1% and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
Strides Pharma Inc.
East Brunswick, NJ 08816

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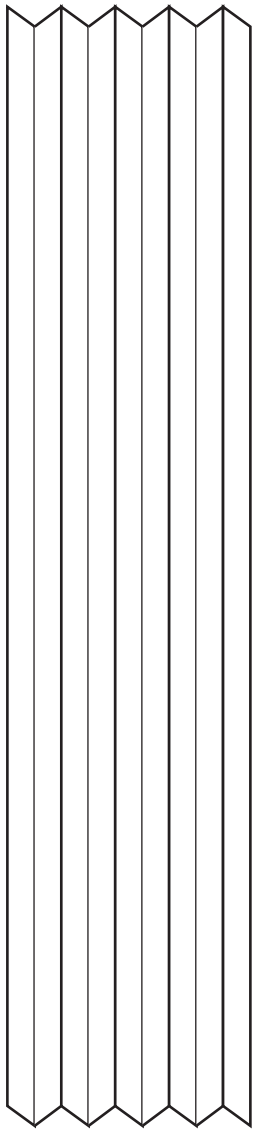
PLATINUM PRESS

Fold Pattern

Diagrams Below Are Not to Scale

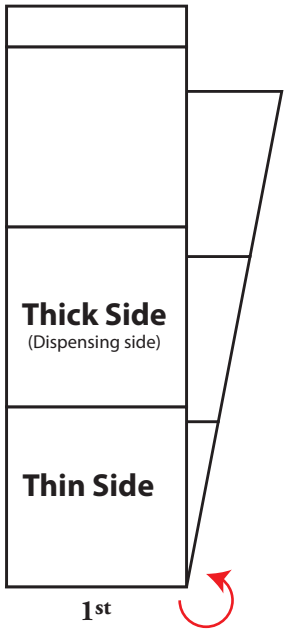
Parallel Folds

#of Panels: 9

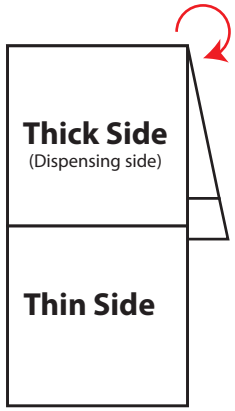


Right Angle (RT) Folds

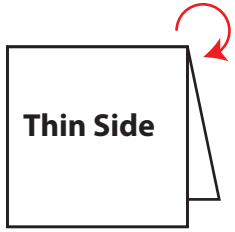
#of Panels: 7



1st RT Fold



2nd RT Fold



3rd RT Fold

Rev: 4