21136

TESTOSTERONE
Gel for Topical Use CIII

TESTOSTERONE
Gel for Topical Use CIII

21136

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TESTOSTERONE gel for topical use CIII

Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

See full prescribing information for complete boxed warning.

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

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

Testosterone gel 1.62% 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 1.62% in men with "age-related hypogonadism" have not been established. (1)
- Safety and efficacy of testosterone gel 1.62% in males less than 18 years old have not been established. (1, 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 1.62% differs from testosterone gel 1%. For dosage and administration of testosterone gel 1% refer to its full prescribing information. (2)**
- Prior to initiating testosterone gel 1.62%, 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 1.62% is 40.5 mg of testosterone (2 pump actuations), applied topically once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of the shoulders and upper arms. Do not apply testosterone gel 1.62% to any other parts of the body including the abdomen, genitals, chest, armpits (axillae), or knees. (2.2, 12.3)
- Dose adjustment: Testosterone gel 1.62% can be dose adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation) and a maximum of 81 mg of testosterone (4 pump actuations). The dose should be titrated based on the pre-dose morning serum testosterone concentration at approximately 14 days and 28 days after starting treatment or following dose adjustment. Additionally, serum testosterone concentration should be assessed periodically thereafter. (2.1)
- Patients should wash hands immediately with soap and water after applying testosterone gel 1.62% 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 1.62% for topical use is available as follows:

- a metered-dose pump that delivers 20.25 mg testosterone per actuation. (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 1.62%. Secondary exposure to testosterone can produce signs of virilization. Testosterone gel 1.62% 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)
- 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 1.62% is flammable until dry (5.16)

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

The most common adverse reaction (incidence ≥ 5%) is an increase in prostate specific antigen (PSA). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TWi Pharmaceuticals, Inc. at 1-844-518-2989 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 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 1.62% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2019

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 1.62% 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 1.62% in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- Safety and efficacy of testosterone gel 1.62% in males less than 18 years old have not been established [see *Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure *[see Indications and Usage (1), and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

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

Prior to initiating testosterone gel 1.62%, 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 1.62% is 40.5 mg of testosterone (2 pump actuations) applied topically once daily in the morning to the shoulders and upper arms.

The dose can be adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation) and a maximum of 81 mg of testosterone (4 pump actuations). To ensure proper dosing, the dose should be titrated based on the pre-dose morning serum testosterone concentration from a single blood draw at approximately 14 days and 28 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter. Table 1 describes the dose adjustments required at each titration step.

Table 1: Dose Adjustment Criteria

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue on current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation)

The application site and dose of testosterone gel 1.62% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

- Testostrone gel 1.62% should be applied to clean, dry, intact skin of the upper arms and shoulders. Do not apply testostrone gel 1.62% to any other parts of the body, including the abdomen, genitals, chest, armpits (axillae), or knees *[see Clinical Pharmacology (12.3)]*. Area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt. Patients should be instructed to use the palm of the hand to apply testostrone gel 1.62% and spread across the maximum surface area as directed in Table 2 and in Figure 1.

Table 2: Application Sites for Testosterone Gel 1.62%, Pump

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0
40.5 mg	2	1	1
60.75 mg	3	2	1
81 mg	4	2	2

The prescribed daily dose of testosterone gel 1.62% should be applied to the right and left upper arms and shoulders as shown in the shaded areas in Figure 1.

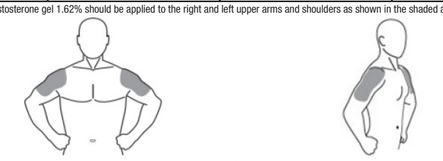


Figure 1. Application Sites for Testosterone Gel 1.62%

Once the application site is dry, the site should be covered with clothing *[see Clinical Pharmacology (12.3)]*. Wash hands thoroughly with soap and water. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including testosterone gel 1.62%, are flammable.

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

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After the priming procedure, fully depress the actuator once for every 20.25 mg of testosterone gel 1.62%. Testosterone gel 1.62% should be delivered directly into the palm of the hand and then applied to the application sites.

Alternatively, testosterone gel 1.62% can be applied directly to the application sites from the pump.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from testosterone gel 1.62%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using testosterone gel 1.62%.
- Testosterone gel 1.62% should only be applied to the upper arms and shoulders. The area of application should be limited to the area that will be covered by a short sleeve t-shirt.
- Patients should wash their hands with soap and water immediately after applying testosterone gel 1.62%.
- Patients should cover the application site(s) with clothing (e.g., a t-shirt) after the gel has dried.
- Prior to situations in which direct skin-to-skin contact is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which testosterone gel 1.62% 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 1.62% for topical use only, is available as follows:

- A metered-dose pump. Each pump actuation delivers 20.25 mg of testosterone in 1.25 g of gel.

4 CONTRAINDICATIONS

- Testosterone gel 1.62% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.
- Testosterone gel 1.62% is contraindicated in women who are pregnant. Testosterone gel 1.62% 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 1.62%. If a pregnant woman is exposed to testosterone gel 1.62%, 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. Evaluation of patients for prostate cancer prior to initiating and during treatment with androgens is appropriate *[see Contraindications (4)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance 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 1.62% *[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 1.62%. 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 1.62% 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 1.62%.

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 the lack of controlled evaluations in women and potential virilizing effects, testosterone gel 1.62% 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 1.62%, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading 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 1.62% is not known to cause these adverse effects.

5.10 Edema

Androgens, including testosterone gel 1.62%, 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 1.62%, 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.

5.13 Lipids

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

5.14 Hypercalcemia

Androgens, including testosterone gel 1.62 %, 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 1.62%, 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 1.62%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the testosterone gel 1.62% 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.

Testosterone gel 1.62% was evaluated in a two-phase, 364-day, controlled clinical study. The first phase was a multi-center, randomized, double-blind, parallel-group, placebo-controlled period of 182 days, in which 234 hypogonadal men were treated with testosterone gel 1.62% and 40 received placebo. Patients could continue in an open-label, non-comparative, maintenance period for an additional 182 days *[see Clinical Studies (14.1)]*.

The most common adverse reaction reported in the double-blind period was increased prostate specific antigen (PSA) reported in 26 testosterone gel 1.62%-treated patients (11.1%). In 17 patients, increased PSA was considered an adverse event by meeting one of the two pre-specified criteria for abnormal PSA values, defined as (1) average serum PSA >4 ng/mL based on two separate determinations, or (2) an average change from baseline in serum PSA of greater than 0.75 ng/mL on two determinations.

During the 182-day, double-blind period of the clinical trial, the mean change in serum PSA value was 0.14 ng/mL for patients receiving testosterone gel 1.62% and -0.12 ng/mL for the patients in the placebo group. During the double-blind period, seven patients had a PSA value >4.0 ng/mL, four of these seven patients had PSA less than or equal to 4.0 ng/mL upon repeat testing. The other three patients did not undergo repeat PSA testing.

During the 182-day, open-label period of the study, the mean change in serum PSA values was 0.10 ng/mL for both patients continuing on active therapy and patients transitioning onto active from placebo. During the open-label period, three patients had a serum PSA value > 4.0 ng/mL, two of whom had a serum PSA less than or equal to 4.0 ng/mL upon repeated testing. The other patient did not undergo repeat PSA testing. Among previous placebo patients, 3 of 28 (10.7%), had increased PSA as an adverse event in the open-label period.

Table 3 shows adverse reactions reported by >2% of patients in the 182-day, double-blind period of the testosterone gel 1.62% clinical trial and more frequent in the testosterone gel 1.62% treated group versus placebo.

Table 3: Adverse Reactions Reported in >2% of Patients in the 182-Day, Double-Blind Period of Testosterone Gel 1.62% Clinical Trial

	Number (%) of Patients	
Adverse Reaction	**Testosterone Gel 1.62% N=234**	**Placebo N=40**
PSA increased*	26 (11.1%)	0%
Emotional lability**	6 (2.6%)	0%
Hypertension	5 (2.1%)	0%
Hematocrit or hemoglobin increased	5 (2.1%)	0%
Contact dermatitis***	5 (2.1%)	0%
***PSA increased** includes: PSA values that met pre-specified criteria for abnormal PSA values (an average change from baseline > 0.75 ng/mL and/or an average PSA value >4.0 ng/mL based on two measurements) as well as those reported as adverse events.		
****Emotional lability** includes: mood swings, affective disorder, impatience, anger, and aggression.		
*****Contact dermatitis** includes: 4 patients with dermatitis at non-application sites.		

Other adverse reactions occurring in less than or equal to 2% of testosterone gel 1.62%-treated patients and more frequently than placebo included: frequent urination, and hyperlipidemia.

In the open-label period of the study (N=191), the most commonly reported adverse reaction (experienced by greater than 2% of patients) was increased PSA (n=13; 6.2%) and sinusitis. Other adverse reactions reported by less than or equal to 2% of patients included increased hemoglobin or hematocrit, hypertension, acne, libido decreased, insomnia, and benign prostatic hypertrophy.

During the 182-day, double-blind period of the clinical trial, 25 testosterone gel 1.62%-treated patients (10.7%) discontinued treatment because of adverse reactions. These adverse reactions included 17 patients with PSA increased and 1 report each of: hematocrit increased, blood pressure increased, frequent urination, diarrhea, fatigue, pituitary tumor, dizziness, skin erythema and skin nodule (same patient – neither at application site), vasovagal syncope, and diabetes mellitus. During the 182-day, open-label period, 9 patients discontinued treatment because of adverse reactions. These adverse reactions included 6 reports of PSA increased, 2 of hematocrit increased, and 1 each of triglycerides increased and prostate cancer.

Application Site Reactions

In the 182-day double-blind period of the study, application site reactions were reported in two (2/234; 0.9%) patients receiving testosterone gel 1.62%, both of which resolved. Neither of these patients discontinued the study due to application site adverse reactions. In the open-label period of the study, application site reactions were reported in three (3/219; 1.4%) additional patients that were treated with testosterone gel 1.62%. None of these subjects were discontinued from the study due to application site reactions.

MEDICATION GUIDE

TESTOSTERONE (tes-TOS-ter-one) GEL CIII 1.62% for topical use

What is the most important information I should know about TESTOSTERONE GEL 1.62%?

1 TESTOSTERONE GEL 1.62% 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 1.62% 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 1.62%.

Children

Signs and symptoms of early puberty in a child when they come in direct contact with TESTOSTERONE GEL 1.62% 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 1.62% may include:

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

Stop using TESTOSTERONE GEL 1.62% 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 1.62%.

2 To lower the risk of transfer of TESTOSTERONE GEL 1.62% from your body to others, follow these important instructions:

- o Apply TESTOSTERONE GEL 1.62% only to your shoulders and upper arms that will be covered by a short sleeve t-shirt.
- o Wash your hands right away with soap and water after applying TESTOSTERONE GEL 1.62%.
- o After the gel has dried, cover the application area with clothing. Keep the area covered until you have washed the application area well or have showered.
- o If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.
- o If a child or woman touches the area where you have applied TESTOSTERONE GEL 1.62%, that area on the child or woman should be washed well with soap and water right away.

What is TESTOSTERONE GEL 1.62%?

TESTOSTERONE GEL 1.62% is a prescription medicine that contains testosterone. TESTOSTERONE GEL 1.62% 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 1.62%.
- It is not known if TESTOSTERONE GEL 1.62% is safe or effective to treat men who have low testosterone due to aging.
- It is not known if TESTOSTERONE GEL 1.62% is safe or effective in children younger than 18 years old. Improper use of TESTOSTERONE GEL 1.62% may affect bone growth in children.

TESTOSTERONE GEL 1.62% is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your TESTOSTERONE GEL 1.62% in a safe place to protect it. Never give your TESTOSTERONE GEL 1.62% 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 1.62% is not meant for use in women.

Do not use TESTOSTERONE GEL 1.62% if you:
- have breast cancer.
- have or might have prostate cancer.
- are pregnant. TESTOSTERONE GEL 1.62% may harm your unborn baby.
- Women who are pregnant should avoid contact with the area of skin where TESTOSTERONE GEL 1.62% has been applied.

Before using TESTOSTERONE GEL 1.62%, 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 kidney or liver 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 1.62% with certain other medicines can affect each other.

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

How should I use TESTOSTERONE GEL 1.62%?

- See the detailed **Instructions for Use** about how to use TESTOSTERONE GEL 1.62% at the end of this Medication Guide.
- It is important that you apply TESTOSTERONE GEL 1.62% exactly as your healthcare provider tells you to.
- Your healthcare provider may change your TESTOSTERONE GEL 1.62% dose. **Do not** change your TESTOSTERONE GEL 1.62% dose without talking to your healthcare provider.
- Apply TESTOSTERONE GEL 1.62% at the same time each morning. TESTOSTERONE GEL 1.62% should be applied after showering or bathing.

What are the possible side effects of TESTOSTERONE GEL 1.62%?

TESTOSTERONE GEL 1.62% can cause serious side effects including:

See **"What is the most important information I should know about TESTOSTERONE GEL 1.62%?"**

- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using TESTOSTERONE GEL 1.62%.** This can include:
  - o increased urination at night.
  - o trouble starting your urine stream.
  - o having to pass urine many times during the day.
  - o having an urge to go to the bathroom right away.
  - o having a urine accident.
  - o 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 1.62%.

- **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 1.62% 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 1.62% include:

- increased prostate specific antigen (a test used to screen for prostate cancer)
- mood swings
- hypertension
- increased red blood cell count
- skin irritation where TESTOSTERONE GEL 1.62% is applied

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 1.62%. 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 1.62%

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TESTOSTERONE GEL 1.62% for a condition for which it was not prescribed. Do not give TESTOSTERONE GEL 1.62% 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 1.62% that is written for health professionals.

What are the ingredients in TESTOSTERONE GEL 1.62%?

Active ingredient: testosterone

Inactive ingredients: isopropyl myristate, carbomer homopolymer type C, sodium hydroxide, ethyl alcohol 75.5% v/v, and purified water.

For more information about TESTOSTERONE GEL 1.62%, call 1-844-518-2989 or go to www.twipharma.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 05/19

INSTRUCTIONS FOR USE

TESTOSTERONE GEL CIII

1.62%

for topical use

Read this Instructions for Use for TESTOSTERONE GEL 1.62% 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 1.62%:

- **TESTOSTERONE GEL 1.62% comes in a pump.**
- **Before applying TESTOSTERONE GEL 1.62% make sure that your shoulders and upper arms are clean, dry, and that there is no broken skin.**
- **TESTOSTERONE GEL 1.62% is to be applied to the area of your shoulders and upper arms that will be covered by a short sleeve t-shirt (See Figure A).** Do not apply TESTOSTERONE GEL 1.62% to any other parts of your body such as your stomach area (abdomen), penis, scrotum, chest, armpits (axillae), or knees.

(Figure A)

If you are using TESTOSTERONE GEL 1.62% pump:

- Before using a new bottle of TESTOSTERONE GEL 1.62 % for the first time, you will need to remove the cap and then prime the pump. To prime the TESTOSTERONE GEL 1.62% pump, slowly push the pump all the way down 3 times, over the sink drain. **Do not** use any TESTOSTERONE GEL 1.62% that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your TESTOSTERONE GEL 1.62% pump is now ready to use.
- Remove the cap from the pump. Then, put the spout opening at the top of the pump where the medicine comes out over the palm of your hand and slowly push the pump all the way down. Apply TESTOSTERONE GEL 1.62% to the application site. You may also apply TESTOSTERONE GEL 1.62% directly to the application site. **Your healthcare provider will tell you the number of times to press the pump for each dose.**
- **Wash your hands with soap and water right away.**

Find Your Dose as Prescribed by Your Healthcare Provider		Application Method
1 Pump	20.25 mg	Apply 1 pump of TESTOSTERONE GEL 1.62% to 1 upper arm and shoulder.
2 Pumps	40.5 mg	Apply 1 pump of TESTOSTERONE GEL 1.62% to 1 upper arm and shoulder and then apply 1 pump of TESTOSTERONE GEL 1.62% to the opposite upper arm and shoulder.
3 Pumps	60.75 mg	Apply 2 pumps of TESTOSTERONE GEL 1.62% to 1 upper arm and shoulder and then apply 1 pump of TESTOSTERONE GEL 1.62% to the opposite upper arm and shoulder.
4 Pumps	81 mg	Apply 2 pumps of TESTOSTERONE GEL 1.62% to 1 upper arm and shoulder and then apply 2 pumps of TESTOSTERONE GEL 1.62% to the opposite upper arm and shoulder.

How should I store TESTOSTERONE GEL 1.62%?

- Store TESTOSTERONE GEL 1.62% at 59ºF to 86ºF (15ºC to 30ºC).
- When it is time to throw away the pump, safely throw away used TESTOSTERONE GEL 1.62% in household trash. Be careful to prevent accidental exposure of children or pets.
- Keep TESTOSTERONE GEL 1.62% away from fire.

Keep TESTOSTERONE GEL 1.62% and all medicines out of the reach of children.

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

Manufactured for:
TWi Pharmaceuticals USA, Inc.
Paramus, NJ 07652

Manufactured by:

TWi Pharmaceuticals, Inc.
Taoyuan City, 32063, Taiwan

Revised: 05/19

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 4).

Table 4: Adverse Reactions from Post Approval Experience of Testosterone Gel 1% by System Organ Class

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders:	Elevated hemoglobin or hematocrit, polycythemia, anemia
Cardiovascular disorders:	Myocardial infarction, stroke
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination*
Hepatobiliary disorders:	Abnormal liver function tests
Investigations:	Lab test abnormal**, elevated PSA, electrolyte changes (nitrogen, calcium, potassium [includes hypokalemia], phosphorus, sodium), impaired glucose tolerance, hyperlipidemia, HDL, fluctuating testosterone levels, weight increase
Neoplasms:	Prostate cancer
Nervous system disorders:	Dizziness, headache, insomnia, sleep apnea
Psychiatric disorders:	Amnesia, anxiety, depression, hostility, emotional lability, decreased libido, nervousness
Reproductive system and breast disorders:	Gynecomastia, mastodynia, oligospermia, priapism (frequent or prolonged erections), prostate enlargement, BPH, testis disorder***
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (discolored hair, dry skin, erythema, paresthesia, pruritus, rash), skin dry, pruritus, sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes), venous thromboembolism
***Impaired urination* includes** nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream	
****Lab test abnormal* includes** elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, or elevated serum creatinine	
*****Testis disorder* includes** atrophy or non-palpable testis, varicocele, testis sensitivity or tenderness	

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 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 1.62% 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 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 1.62% 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 1.62% *[see Adverse Reactions (6.1, 6.2)]*.

During treatment with large doses of exogenous androgens, including testosterone gel 1.62%, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitarytesticular 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 effectiveness of testosterone gel 1.62% 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 1.62% to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 234 patients enrolled in the clinical trial utilizing testosterone gel 1.62%, 21 were over 65 years of age. Additionally, there is insufficient long-term safety data in geriatric patients to assess the potentially increased risks of cardiovascular disease and prostate cancer.

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

8.6 Renal Impairment

No studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Testosterone gel 1.62% 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

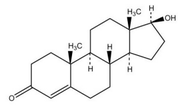
There is a single report of acute overdosage after parenteral administration of an approved testosterone product in the literature. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident. There were no reports of overdosage in the testosterone gel 1.62% clinical trial.

Treatment of overdosage would consist of discontinuation of testosterone gel 1.62%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

11 DESCRIPTION

Testosterone gel 1.62% for topical use is a clear, colorless gel containing testosterone. Testosterone is an androgen. Testosterone gel 1.62% is available in a metered-dose pump.

The active pharmacologic ingredient in testosterone gel 1.62% is testosterone. Testosterone USP is a white to almost white 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

The inactive ingredients in testosterone gel 1.62% are: isopropyl myristate, carbomer homopolymer type C, sodium hydroxide, ethyl alcohol 75.5% v/v, and purified water.

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; and alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has 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 1.62%.

12.3 Pharmacokinetics

Absorption

Testosterone gel 1.62% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (300 – 1000 ng/dL) seen in healthy men. Testosterone gel 1.62% provides continuous transdermal delivery of testosterone for 24 hours following once daily application to clean, dry, intact skin of the shoulders and upper arms. Average serum testosterone concentrations over 24 hours (C_{avg}) observed when testosterone gel 1.62% was applied to the upper arms/shoulders were comparable to average serum testosterone concentrations (C_{avg}) when testosterone gel 1.62% was applied using a rotation method utilizing the abdomen and upper arms/ shoulders. The rotation of abdomen and upper arms/shoulders was a method used in the pivotal clinical trial [see *Clinical Studies (14.1)*].

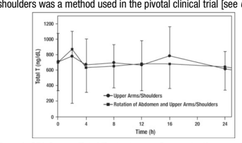


Figure 2: Mean (±SD) Serum Total Testosterone Concentrations on Day 7 in Patients Following Testosterone Gel 1.62% Once-Daily Application of 81 mg of Testosterone (N=33) for 7 Days

Distribution

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

Metabolism

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

Excretion

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

When testosterone gel 1.62% treatment is discontinued, serum testosterone concentrations return to approximately baseline concentrations within 48-72 hours after administration of the last dose.

Potential for testosterone transfer

The potential for testosterone transfer following administration of testosterone gel 1.62% when it was applied only to upper arms/shoulders was evaluated in two clinical studies of males dosed with testosterone gel 1.62% and their untreated female partners. In one study, 8 male subjects applied a single dose of testosterone gel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes. Serum concentrations of testosterone were monitored in female subjects for 24 hours after contact occurred. After direct skin-to-skin contact with the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 280% and 267%, respectively, compared to mean baseline testosterone concentrations. In a second study evaluating transfer of testosterone, 12 male subjects applied a single dose of testosterone gel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes while the site of application was covered by a t-shirt. When a t-shirt was used to cover the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 6% and 11%, respectively, compared to mean baseline testosterone concentrations.

A separate study was conducted to evaluate the potential for testosterone transfer from 16 males dosed with testosterone gel 1.62% 81 mg when it was applied to abdomen only for 7 days, a site of application not approved for testosterone gel 1.62%. Two (2) hours after application to the males on each day, the female subjects rubbed their abdomens for 15 minutes to the abdomen of the males. The males had covered the application area with a T-shirt. The mean testosterone C_{avg} and C_{max} in female subjects on day 1 increased by 43% and 47%, respectively, compared to mean baseline testosterone concentrations. The mean testosterone C_{avg} and C_{max} in female subjects on day 7 increased by 60% and 58%, respectively, compared to mean baseline testosterone concentrations.

Effect of showering

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 24 hypogonadal men, the effect of showering on testosterone exposure was assessed after once daily application of testosterone gel 1.62% 81 mg to upper arms/shoulders for 7 days in each treatment period. On the 7th day of each treatment period, hypogonadal men took a shower with soap and water at either 2, 6, or 10 hours after drug application. The effect of showering at 2 or 6 hours post-dose on Day 7 resulted in 13% and 12% decreases in mean C_{avg}, respectively, compared to Day 6 when no shower was taken after drug application. Showering at 10 hours after drug application had no effect on bioavailability. The amount of testosterone remaining in the outer layers of the skin at the application site on the 7th day was assessed using a tape stripping procedure and was reduced by at least 80% after showering 2-10 hours post-dose compared to on the 6th day when no shower was taken after drug application.

Effect of hand washing

In a randomized, open-label, single-dose, 2-way crossover study in 16 healthy male subjects, the effect of hand washing on the amount of residual testosterone on the hands was evaluated. Subjects used their hands to apply the maximum dose (81 mg testosterone) of testosterone gel 1.62% to their upper arms and shoulders. Within 1 minute of applying the gel, subjects either washed or did not wash their hands prior to study personnel wiping the subjects' hands with ethanol dampened gauze pads. The gauze pads were then analyzed for residual testosterone content. A mean (SD) of 0.1 (0.04) mg of residual testosterone (0.12% of the actual applied dose of testosterone, and a 96% reduction compared to when hands were not washed) was recovered after washing hands with water and soap.

Effect of sunscreen or moisturizing lotion on absorption of testosterone

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 18 hypogonadal males, the effect of applying a moisturizing lotion or a sunscreen on the absorption of testosterone was evaluated with the upper arms/shoulders as application sites. For 7 days, moisturizing lotion or sunscreen (SPF 50) was applied daily to the testosterone gel 1.62% application site 1 hour after the application of testosterone gel 1.62% 40.5 mg. Application of moisturizing lotion increased mean testosterone C_{avg} and C_{max} by 14% and 17%, respectively, compared to testosterone gel 1.62% administered alone. Application of sunscreen increased mean testosterone C_{avg} and C_{max} by 8% and 13%, respectively, compared to testosterone gel 1.62% applied alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Clinical Trials in Hypogonadal Males

Testosterone gel 1.62% was evaluated in a multi-center, randomized, double-blind, parallel-group, placebo-controlled study (182-day double-blind period) in 274 hypogonadal men with body mass index (BMI) 18-40 kg/m^2 and 18-80 years of age (mean age 53.8 years). The patients had an average serum testosterone concentration of <300 ng/dL, as determined by two morning samples collected on the same visit. Patients were Caucasian 83%, Black 13%, Asian or Native American 4%. 7.5% of patients were Hispanic.

Patients were randomized to receive active treatment or placebo using a rotation method utilizing the abdomen and upper arms/shoulders for 182 days. All patients were started at a daily dose of 40.5 mg (two pump actuations) testosterone gel 1.62% or matching placebo on Day 1 of the study. Patients returned to the clinic on Day 14, Day 28, and Day 42 for predose serum total testosterone assessments. The patient's daily dose was titrated up or down in 20.25 mg increments if the predose serum testosterone value was outside the range of 350-750 ng/dL. The study included four active testosterone gel 1.62% doses: 20.25 mg, 40.5 mg, 60.75 mg, and 81 mg daily.

The primary endpoint was the percentage of patients with C_{avg} within the normal range of 300-1000 ng/dL on Day 112. In patients treated with testosterone gel 1.62%, 81.6% (146/179) had C_{avg} within the normal range at Day 112. 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 112 were 11.2% and 5.5%, respectively. Two patients had a C_{max} >2500 ng/dL on Day 112 (2510 ng/dL and 2550 ng/dL, respectively); neither of these 2 patients demonstrated an abnormal C_{max} on prior or subsequent assessments at the same dose.

Patients could agree to continue in an open-label, active treatment maintenance period of the study for an additional 182 days.

Dose titrations on Days 14, 28, and 42 resulted in final doses of 20.25 mg – 81 mg on Day 112 as shown in Table 5.

Table 5: Mean (SD) Testosterone Concentrations (C_{avg} and C_{max}) by final dose on Days 112 and 364

Parameter	Final Dose on Day 112					
	Placebo (n=27)	**20.25 mg (n=12)**	**40.5 mg (n=34)**	**60.75 mg (n=54)**	**81 mg (n=79)**	**All Active (n=179)**
C_{avg} (ng/dL)	303 (135)	457 (275)	524 (228)	643 (285)	537 (240)	561 (259)
C_{max} (ng/dL)	450 (349)	663 (473)	798 (439)	958 (497)	813 (479)	845 (480)
	Final Dose on Day 364					
		20.25 mg (n=7)	**40.5 mg (n=26)**	**60.75 mg (n=29)**	**81 mg (n=74)**	**Continuing Active (n=136)**
C_{avg} (ng/dL)		386 (130)	474 (176)	513 (222)	432 (186)	455 (192)
C_{max} (ng/dL)		562 (187)	715 (306)	839 (568)	649 (329)	697 (389)

Figure 3 summarizes the pharmacokinetic profile of total testosterone in patients completing 112 days of testosterone gel 1.62% treatment administered as a starting dose of 40.5 mg of testosterone (2 pump actuations) for the initial 14 days followed by possible titration according to the follow-up testosterone measurements.

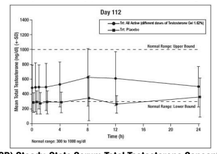


Figure 3: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 112

Efficacy was maintained in the group of men that received testosterone gel 1.62% for one full year. In that group, 78% (106/136) had average serum testosterone concentrations in the normal range at Day 364. Figure 4 summarizes the mean total testosterone profile for these patients on Day 364.

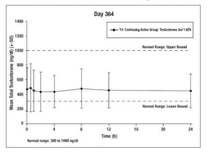


Figure 4: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 364

The mean estradiol and DHT concentration profiles paralleled the changes observed in testosterone. The levels of LH and FSH decreased with testosterone treatment. The decreases in levels of LH and FSH are consistent with reports published in the literature of long-term treatment with testosterone.

16 HOW SUPPLIED/STORAGE AND HANDLING

Testosterone gel 1.62% is supplied in non-aerosol, metered-dose pumps that deliver 20.25 mg of testosterone per complete pump actuation as clear, colorless gel. The pumps are composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations; each pump actuation dispenses 1.25 g of gel.

NDC Number	Package Size
24979-078-15	88 g pump (each pump dispenses 60 metered pump actuations with each pump actuation containing 20.25 mg of testosterone in 1.25 g of gel)

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Used testosterone gel 1.62% pumps 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 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 1.62% *[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 1.62% 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 1.62% in men *[see Medication Guide]*:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using testosterone gel 1.62%.
- Patients using testosterone gel 1.62% should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water immediately after application.
  - **Cover the application site(s)** with clothing after the gel has dried.
  - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
- In the event that unwashed or unclothed skin to which testosterone gel 1.62% 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 the urine stream, passing 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 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 1.62% therapy and to reread it each time the prescription is renewed.**
- **Testosterone gel 1.62% should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women.**
- Keep testostetone gel 1.62% out of the reach of children.
- **Testosterone gel 1.62% 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 1.62% is prescribed to meet the patient's specific needs; therefore, the patient should never share testostetone gel 1.62% with anyone.
- Wait 2 hours before swimming or washing following application of testostetone gel 1.62%. This will ensure that the greatest amount of testostetone gel 1.62% is absorbed into their system.

Manufactured for:
TWi Pharmaceuticals USA, Inc.
Paramus, NJ 07652

Manufactured by:

TWi Pharmaceuticals, Inc.
Taoyuan City, 32063, Taiwan

Revised: 03/19

DRAWING #31370
19.25 X 17.16

Proof A B C D (E) F G

PLEASE SIGN AND RETURN

☑ OK to Print

☐ Send Another Proof

Signature Chingju Tseng Date

Digitally signed by chingju.tseng@twipharma.com
DN: cn=chingju.tseng@twipharma.com, email=chingju.tseng@twipharma.com
Reason: I am approving this document
Date: 2019.11.15 ~~13:53:16 -08'00'~~
Adobe Acrobat Reader version: 2019.021.20049

Job No. P426953 **Item No.** 21136

Date Sent 11-12-19 Date Returned

☐ Art Sent ☐ Art Returned

This proof is printed on proof paper and is not intended to show the paper or the ink used on the finished job.

PLEASE READ PROOF CAREFULLY FOR ERRORS

If proof is correct, check "OK to Print" box, sign and date it. If changes are needed, show such changes clearly in the margin of the proof, check "Send Another Proof" box, sign and date it. We cannot assume responsibility for corrections other than those indicated on proof.

If the copy as originally submitted is changed when the proof is returned, the changes in the copy are considered alterations. Alterations will be an additional charge.

PLEASE RETURN COPY WITH PROOF

COLBERT PACKAGING

CORPORATE HEADQUARTERS/ FOLDING CARTON PLANT

28355 North Bradley Road, Lake Forest, Illinois 60045

Tel: (847) 367-5990 Fax: (847) 367-4403

FLEXOGRAPHIC PRINTING PLANT

9949 58th Place, Kenosha, Wisconsin 53144

Tel: (262) 925-4740 Fax: (262) 925-4749

Form 131R3

Operator	Init.	Date
Proofer 1	Init.	Date
Proofer 2	Init.	Date

JOB HISTORY:

PROOF A	**Corrections - Customer copy change.**
PROOF B	**Corrections - Customer copy change.**
PROOF C	**Corrections - Customer copy change.**
PROOF D	**Corrections - Customer copy change.**

3% 25% 50% 75% 100%

SCREEN ANGLE +45

BLACK