

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANDROGEL 1.62% safely and effectively. See full prescribing information for ANDROGEL 1.62%.

AndroGel® (testosterone gel) 1.62% for topical use CIII
Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

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

INDICATIONS AND USAGE

AndroGel 1.62% is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

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

Important limitations of use: Safety and efficacy of AndroGel 1.62% in males <18 years old have not been established. (1, 8.4)

DOSAGE AND ADMINISTRATION

- **Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)**
- Starting dose of AndroGel 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 AndroGel 1.62% to any other parts of the body including the abdomen or genitals. (2.2, 12.3)
- Dose adjustment: AndroGel 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 AndroGel 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)
- AndroGel 1.62% is not interchangeable with other topical testosterone products. (2.1)

DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1.62% for topical use is available as a metered-dose pump. One pump actuation delivers 20.25 mg of testosterone. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1)
- Avoid unintentional exposure of women or children to AndroGel 1.62%. Secondary exposure to testosterone can produce signs of virilization. AndroGel 1.62% should be discontinued until the cause of virilization is identified (5.2)
- Exogenous administration of androgens may lead to azoospermia (5.5)
- Edema with or without congestive heart failure (CHF) may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.7)
- Sleep apnea may occur in those with risk factors (5.9)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.6, 5.10)
- AndroGel 1.62% is flammable until dry (5.13)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-241-1643 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 AndroGel 1.62% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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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

AndroGel 1.62% is an androgen 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): idiopathic 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.

Important limitations of use: Safety and efficacy of AndroGel 1.62% in males <18 years old have not been established [See *Use in Specific Populations* (8.4)].

2 DOSAGE AND ADMINISTRATION

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

2.1 Dosing and Dose Adjustment

The recommended starting dose of AndroGel 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 AndroGel 1.62% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AndroGel 1.62% should be applied to clean, dry, intact skin of the upper arms and shoulders. Do not apply AndroGel 1.62% to any other parts of the body, including the abdomen or genitals [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 AndroGel 1.62% and spread across the maximum surface area as directed in Table 2 and in Figure 1.

Table 2: Application Sites for AndroGel 1.62%

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 AndroGel 1.62% should be applied to the right and left upper arms and shoulders as shown in the shaded areas in Figure 1.

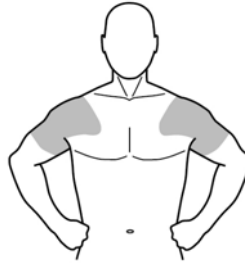


Figure 1. Application Sites for AndroGel 1.62%

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 AndroGel 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 AndroGel 1.62%. AndroGel 1.62% should be delivered directly into the palm of the hand and then applied to the application sites. Alternatively, AndroGel 1.62% can be applied directly to the application sites.

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

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AndroGel 1.62%.
- AndroGel 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 AndroGel 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 AndroGel 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

AndroGel (testosterone gel) 1.62% for topical use only, is supplied in a metered-dose pump. One pump actuation delivers 20.25 mg of testosterone.

4 CONTRAINDICATIONS

- AndroGel 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)].
- AndroGel 1.62% is contraindicated in women who are or may become pregnant, or who are breastfeeding. AndroGel 1.62% may cause fetal harm when administered to a pregnant woman. AndroGel 1.62% may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with AndroGel 1.62%. If a pregnant woman is exposed to AndroGel 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, 8.3)].

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 AndroGel 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 Use in Women

Due to the lack of controlled evaluations in women and potential virilizing effects, AndroGel 1.62% is not indicated for use in women [see *Contraindications (4)* and *Use in Specific Populations (8.1, 8.3)*].

5.5 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AndroGel 1.62%, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading to adverse effects on semen parameters including sperm count.

5.6 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. AndroGel 1.62% is not known to cause these adverse effects.

5.7 Edema

Androgens, including AndroGel 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)*].

5.8 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including AndroGel 1.62%, for hypogonadism.

5.9 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.

5.10 Lipids

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

5.11 Hypercalcemia

Androgens, including AndroGel 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.

5.12 Decreased Thyroxine-binding globulin

Androgens, including AndroGel 1.62%, may decrease concentrations of thyroxine-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.13 Flammability

Alcohol based products, including AndroGel 1.62%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the AndroGel 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.

AndroGel 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 AndroGel 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 AndroGel 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 AndroGel 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 AndroGel 1.62% clinical trial and more frequent in the AndroGel 1.62% treated group versus placebo.

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

Adverse Reaction	Number (%) of Patients	
	AndroGel 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 AndroGel 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 AndroGel 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 AndroGel 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 AndroGel 1.62%. None of these subjects were discontinued from the study due to application site reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AndroGel 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 AndroGel 1% by System Organ Class

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders:	Elevated hemoglobin or hematocrit, polycythemia, anemia
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)

* **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 adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications* (4)]: AndroGel 1.62% is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AndroGel 1.62% is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation [see *Contraindications* (4)].

8.4 Pediatric Use

The safety and effectiveness of AndroGel 1.62% in pediatric patients < 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AndroGel 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 AndroGel 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

AndroGel 1.62% contains testosterone, a Schedule III controlled substance as defined under the Anabolic Steroids Control Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drugs are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of a withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

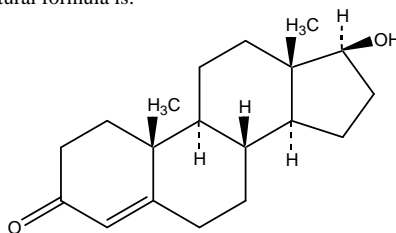
There is a single report of acute overdosage after parenteral administration of an approved testosterone product in the literature. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident. There were no reports of overdosage in the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

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

11 DESCRIPTION

AndroGel 1.62% for topical use is a clear, colorless gel containing testosterone. Testosterone is an androgen. AndroGel 1.62% is available in a metered-dose pump. Each pump actuation provides 20.25 mg of testosterone and each container is capable of dispensing 60 pump actuations. One pump actuation dispenses 1.25 g of gel.

The active pharmacologic ingredient in AndroGel 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 AndroGel 1.62% are: carbopol 980, ethyl alcohol, isopropyl myristate, purified water, and sodium hydroxide.

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 results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia while 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 AndroGel 1.62%.

12.3 Pharmacokinetics

Absorption

AndroGel 1.62% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (300 – 1000 ng/dL) seen in healthy men. AndroGel 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 AndroGel 1.62% was applied to the upper arms/shoulders were comparable to average serum testosterone concentrations (C_{avg}) when AndroGel 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)].

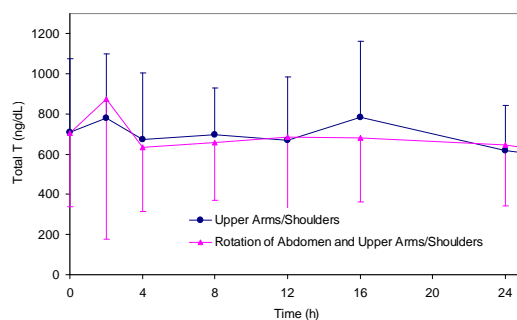


Figure 2: Mean (±SD) Serum Total Testosterone Concentrations on Day 7 in Patients Following AndroGel 1.62% Once-Daily Application of 81 mg of Testosterone (N=33) for 7 Days

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 AndroGel 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 AndroGel 1.62% when it was applied only to upper arms/shoulders was evaluated in two clinical studies of males dosed with AndroGel 1.62% and their untreated female partners. In one study, 8 male subjects applied a single dose of AndroGel 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 AndroGel 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 AndroGel 1.62% 81 mg when it was applied to abdomen only for 7 days, a site of application not approved for AndroGel 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 AndroGel 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 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 AndroGel 1.62% application site 1 hour after the application of AndroGel 1.62% 40.5 mg. Application of moisturizing lotion increased mean testosterone C_{avg} and C_{max} by 14% and 17%, respectively, compared to AndroGel 1.62% administered alone. Application of sunscreen increased mean testosterone C_{avg} and C_{max} by 8% and 13%, respectively, compared to AndroGel 1.62% applied alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, 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. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Hypogonadal Males

AndroGel 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/m² 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) AndroGel 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 AndroGel 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 AndroGel 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					Continuing Active (n=136)
		20.25 mg (n=7)	40.5 mg (n=26)	60.75 mg (n=29)	81 mg (n=74)	
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 AndroGel 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.

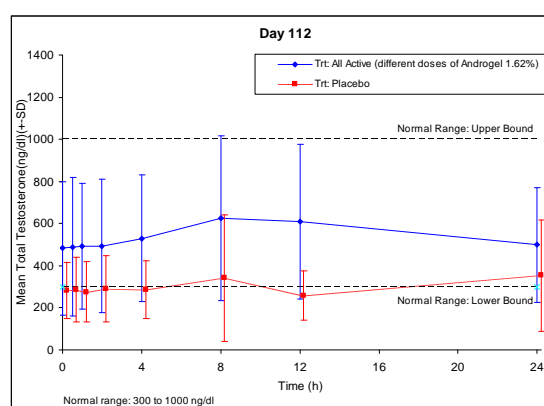


Figure 3: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 112

Efficacy was maintained in the group of men that received AndroGel 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.

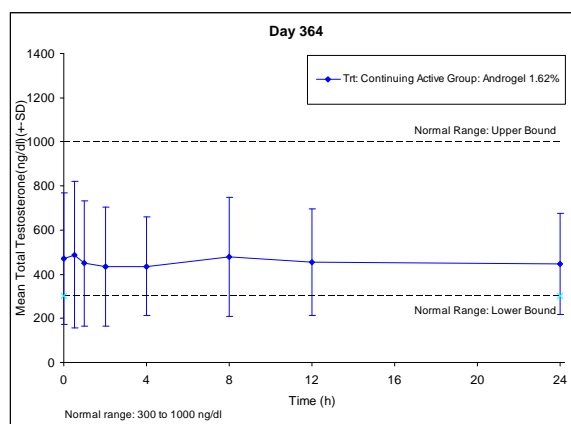


Figure 4: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 364

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

AndroGel 1.62% is supplied in a metered-dose pump that delivers 20.25 mg of testosterone per complete pump actuation. The pump is composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. The metered-dose pump is capable of dispensing 60 metered pump actuations. One pump actuation delivers 1.25 g of gel.

NDC 0051-8462-33

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 AndroGel 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 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 AndroGel 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. 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.
- AndroGel 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 AndroGel 1.62% in men [see *Medication Guide*]:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using AndroGel 1.62%.
- Patients using AndroGel 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 AndroGel 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 AndroGel 1.62% therapy and to reread it each time the prescription is renewed.**
- **AndroGel 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 AndroGel 1.62% out of the reach of children.
- **AndroGel 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.
- AndroGel 1.62% is prescribed to meet the patient's specific needs; therefore, the patient should never share AndroGel 1.62% with anyone.
- Wait 2 hours before swimming or washing following application of AndroGel 1.62%. This will ensure that the greatest amount of AndroGel 1.62% is absorbed into their system.

Marketed by:
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