HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AndroGel® (testosterone gel) 1% 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)**

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

Indications and Usage. (1) 09/2012

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

AndroGel 1% 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% in males less than 18 years old have not been established. (8.4)
- Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure. (1, 12.3)

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

- **Dosage and Administration for AndroGel 1% differs from AndroGel 1.62 %. For dosage and administration of AndroGel 1.62% refer to its full prescribing information. (2)**
- Starting dose of AndroGel 1% is 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet), applied once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply AndroGel 1% to any other parts of the body including the genitals, chest or back. (2.2)
- Dose adjustment: AndroGel 1% can be dose adjusted using 50 mg, 75 mg, or 100 mg of testosterone on the basis of total serum testosterone concentration. The dose should be titrated based on the serum testosterone concentration. Additionally, serum testosterone concentration should be assessed periodically. (2.1)
- Patients should wash hands immediately with soap and water after applying AndroGel 1% and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)

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

AndroGel (testosterone gel) 1% for topical use is available as follows:

- Metered-dose pump that delivers 12.5 mg of testosterone per actuation. (3)
- Packets containing 25 mg of testosterone. (3)
- Packets containing 50 mg of testosterone. (3)

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

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

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

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to AndroGel 1%. Secondary exposure to testosterone can produce signs of virilization. AndroGel 1% 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, 6.2)
- 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% is flammable until dry. (5.13)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

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

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

- There are insufficient long-term safety data in geriatric patients using AndroGel 1% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2013

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

AndroGel 1% 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% in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure (1, 12.3).

2 DOSAGE AND ADMINISTRATION

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

2.1 Dosing and Dose Adjustment

The recommended starting dose of AndroGel 1% is 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet), applied topically once daily in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day).

Dose Adjustment

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

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

2.2 Administration Instructions

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

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

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

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

Multi-Dose Pump

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, patients should completely depress the pump one time actuation for every 12.5 mg of testosterone required to achieve the daily prescribed dosage. The product should be delivered directly into the palm of the hand and then applied to the desired application sites. Alternatively, AndroGel 1% can be applied directly to the application sites. Table 1 provides dosing information for adult males.

Table 1: Dosing Information for AndroGel 1%

Amount of Testosterone	Number of Pump Actuations
50 mg	4 (once daily)
75 mg	6 (once daily)
100 mg	8 (once daily)

Packets

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

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AndroGel 1%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AndroGel 1%.
- Patients should wash hands with soap and water immediately after application of AndroGel 1%.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the gel has dried.
- Prior to situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AndroGel 1% has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

3 DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1% for topical use is available as follows:

- A metered-dose pump. Each pump actuation delivers 12.5 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel.
- A unit dose packet containing 50 mg of testosterone provided in 5 g of gel.

4 CONTRAINDICATIONS

- AndroGel 1% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1), Adverse Reactions (6.1),* and *Nonclinical Toxicology (13.1)]*.
- AndroGel 1% is contraindicated in women who are or may become pregnant, or who are breastfeeding. AndroGel 1% may cause fetal harm when administered to a pregnant woman. AndroGel 1% may cause serious adverse reactions in nursing infants. Exposure of a female 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%. If a pregnant woman is exposed to AndroGel 1%, she should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2)* and *Use in Specific Populations (8.1, 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. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4), Adverse Reactions (6.1)* and *Nonclinical Toxicology (13.1)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AndroGel 1% *[see Dosage and Administration (2.2), Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)]*.

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

5.3 Polycythemia

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

acceptable concentration. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, AndroGel 1% 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%, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

5.6 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% is not known to cause these adverse effects.

5.7 Edema

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

5.8 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including AndroGel 1%, 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 *[see Adverse Reactions (6.2)]*.

5.10 Lipids

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

5.11 Hypercalcemia

Androgens, including AndroGel 1%, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.12 Decreased Thyroxine-binding Globulin

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

5.13 Flammability

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

Clinical Trials in Hypogonadal Men

Table 2 shows the incidence of all adverse events judged by the investigator to be at least possibly related to treatment with AndroGel 1% and reported by >1% of patients in a 180 Day, Phase 3 study.

Table 2: Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel 1% in the 180-Day Controlled Clinical Trial

Adverse Event	Dose of AndroGel 1%		
	50 mg	75 mg	100 mg
	N = 77	N = 40	N = 78
Acne	1%	3%	8%
Alopecia	1%	0%	1%

Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder***	3%	0%	0%

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

**_Prostate disorders_ included five patients with enlarged prostate, one with BPH, and one with elevated PSA results.

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

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

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

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

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

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

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

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

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

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

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

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

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

Increases in Serum PSA Observed in Clinical Trials of Hypogonadal Men

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

Twenty-nine patients (18%) met the per-protocol criterion for increase in serum PSA, defined as >2X the baseline or any single serum PSA >6 ng/mL. Most of these (25/29) met this criterion by at least doubling of their PSA from baseline. In most cases where PSA at least doubled (22/25), the maximum serum PSA value was still <2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%).

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of 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 Drug Reactions from Postmarketing Experience of AndroGel 1% by MedDRA System Organ Class

Blood and the lymphatic system disorders:	Elevated Hgb, Hct (polycythemia)
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders and administration site reactions:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination
Hepatobiliary disorders:	Abnormal liver function tests (e.g. transaminases, elevated GGTP, bilirubin)
Investigations:	Elevated PSA, electrolyte changes (nitrogen, calcium, potassium, phosphorus, sodium), changes in serum lipids (hyperlipidemia, elevated triglycerides, decreased HDL), impaired glucose tolerance, fluctuating testosterone concentrations, weight

	increase
Neoplasms benign, malignant and unspecified (cysts and polyps):	Prostate cancer
Nervous system:	Headache, dizziness, sleep apnea, insomnia
Psychiatric disorders:	Depression, emotional lability, decreased libido, nervousness, hostility, amnesia, anxiety
Reproductive system and breast disorders:	Gynecomastia, mastodynia, prostatic enlargement, testicular atrophy, oligospermia, priapism (frequent or prolonged erections)
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (pruritus, dry skin, erythema, rash, discolored hair, paresthesia), sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes)

Secondary Exposure to Testosterone in Children

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

7 DRUG INTERACTIONS

7.1 Insulin

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

7.2 Oral Anticoagulants

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

7.3 Corticosteroids

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*: AndroGel 1% is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AndroGel 1% is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation *[see Contraindications (4)]*.

8.4 Pediatric Use

The safety and efficacy of AndroGel 1% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

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

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

8.6 Renal Impairment

No studies were conducted in patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AndroGel 1% contains testosterone, a Schedule III controlled substance in the Controlled Substances 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

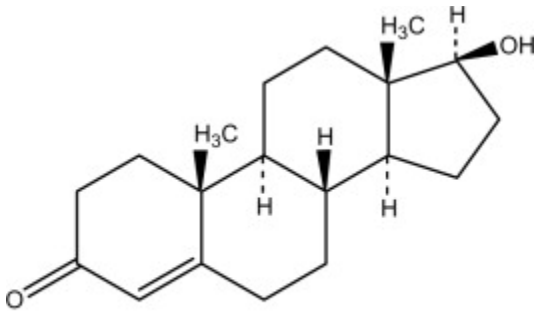
There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone concentrations of up to 11,400 ng/dL with a cerebrovascular accident.

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

11 DESCRIPTION

AndroGel (testosterone gel) 1% is a clear, colorless hydroalcoholic gel containing testosterone.

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



Testosterone

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

Pharmacologically inactive ingredients in AndroGel 1% are carbomer 980, ethanol 67.0%, isopropyl myristate, purified water, and sodium hydroxide. These ingredients are not pharmacologically active.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

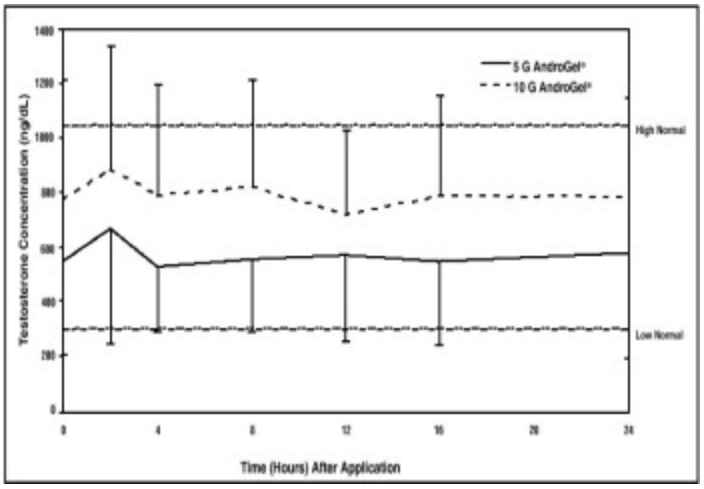
Absorption

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

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

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

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



Distribution

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

Metabolism

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

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

Excretion

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

When AndroGel 1% treatment is discontinued after achieving steady state, serum testosterone concentrations remain in the normal range for 24 to 48 hours but return to their pretreatment concentrations by the fifth day after the last application.

Testosterone Transfer from Male Patients to Female Partners

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

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 Adult Hypogonadal Males

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

patients received treatment in an open-label extension study of AndroGel 1% for an additional period of up to 3 years.

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

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

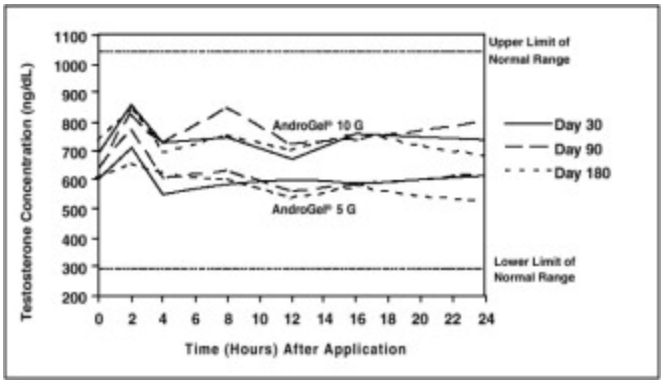


Table 5 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 50 mg, 75 mg, or 100 mg of AndroGel 1%. The 75 mg dose produced mean concentrations intermediate to those produced by 50 mg and 100 mg of AndroGel 1%.

Table 5: Mean (± SD) Steady-State Serum Testosterone Concentrations During Therapy (Day 180)

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

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

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

AndroGel 1% 50 mg/day and 100 mg/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment during the original study. Changes in the 75 mg dose group were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with AndroGel 1% 100 mg.

AndroGel 1% treatment at 50 mg/day and 100 mg/day for 90 days produced significant improvement in libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as assessed by patient responses to a questionnaire). The degree of penile erection as subjectively estimated by the patients, increased with AndroGel 1% treatment, as did the subjective score for "satisfactory duration of erection." AndroGel 1% treatment at 50 mg/day and 100 mg/day produced positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 75 mg dose. DHT concentrations increased in parallel with testosterone concentrations at AndroGel 1% doses of 50 mg/day and 100 mg/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with AndroGel 1% 50 or 100 mg/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of SHBG decreased very slightly (1 to 11%) during AndroGel 1% treatment. In men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and time-dependent manner during treatment with AndroGel 1%.

14.2 Phototoxicity in Humans

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

16 HOW SUPPLIED/STORAGE AND HANDLING

AndroGel 1% is supplied in non-aerosol, metered-dose pumps that deliver 12.5 mg of testosterone per complete pump actuation. 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.

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

NDC Number	Package Size
0051-8488-88	2 x 75 g pump (each pump dispenses 60 metered pump actuations with each pump actuation containing 12.5 mg of testosterone in 1.25 g of gel)
0051-8425-30	30 packets (a unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel)
0051-8450-30	30 packets (a unit dose packet containing 50 mg of testosterone provided in 5 g of gel)

Storage

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

Disposal

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

Patients should be informed of the following:

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

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

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

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel in men. 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% should be promptly discontinued until the cause of virilization is identified

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from testosterone gel in men *[see Medication Guide]*:

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

17.3 Potential Adverse Reactions with Androgens

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

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

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

- **Read the Medication Guide before starting AndroGel 1% therapy and to reread it each time the prescription is renewed**
- **AndroGel 1% 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% out of the reach of children**
- **AndroGel 1% is an alcohol based product and is flammable; therefore avoid fire, flame or smoking until the gel has dried**
- **It is important to adhere to all recommended monitoring**
- **Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood**
- AndroGel 1% is prescribed to meet the patient's specific needs; therefore, the patient should never share AndroGel 1% with anyone.
- Wait 5 hours before swimming or washing following application of AndroGel 1%. This will ensure that the greatest amount of AndroGel 1% is absorbed into their system.

Marketed by:

AbbVie Inc.
North Chicago, IL 60064, USA