

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AndroGel® (testosterone gel) 1% for topical use CIII

Initial U.S. Approval: 1953

INDICATIONS AND USAGE

AndroGel 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) (1.1)
- Hypogonadotropic Hypogonadism (Congenital or Acquired) (1.1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose: 5 g for adult males, applied topically once daily (2.1)
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply AndroGel to the genitals (2.1)
- Dose adjustment for adult males: If serum testosterone level is below the normal range, adjust dose from 5 g to 7.5 g and from 7.5 g to 10 g (2.3)

DOSAGE FORMS AND STRENGTHS

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

- 2 x 75 g pumps (each pump dispenses 60 metered 1.25 g doses) (3)
- 2.5 g packet or 5 g packet (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)

WARNINGS AND PRECAUTIONS

- Patients with benign prostatic hyperplasia (BPH) treated with androgens are at an increased risk for worsening of signs and symptoms of BPH (5.1)
- Cover application site and wash hands to prevent testosterone transfer to others (5.2)
- Due to lack of controlled evaluations in women and potential virilizing effects, AndroGel is not indicated for use in women (5.3)
- Exogenous administration of androgens may lead to azoospermia (5.4)

- Edema may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.6, 6.2)
- Gynecomastia, enlargement of breast, may develop (5.7)
- Sleep apnea may occur in those with risk factors (5.8)
- Monitor serum testosterone, prostatic specific antigen, hemoglobin, hematocrit, liver function test, and lipid levels periodically (2.3, 5.1, 5.9)
- Alcohol-based gels are flammable until dry (5.10)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 5%) are acne, application site reaction, abnormal lab tests, and prostatic disorders. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Solvay Pharmaceuticals, Inc. 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 insulin requirement in diabetic patients (7.1)
- Use of testosterone with ACTH or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.2)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: AndroGel may cause teratogenic effects. AndroGel should not be used in pregnant women. (4, 8.1)
- Nursing mothers should not use AndroGel. (4, 8.3)
- Safety and efficacy of AndroGel in males < 18 years old has not been established (8.4.)
- There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AndroGel to determine whether efficacy in those > 65 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. (8.5)
- No formal studies were conducted involving patients with renal or hepatic insufficiencies (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2007

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FULL PRESCRIBING INFORMATION

Rx only

**1 INDICATIONS AND USAGE****1.1 Testosterone Replacement Therapy**

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

- Primary Hypogonadism (Congenital or Acquired) - testicular failure due to 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 levels and gonadotropins (FSH, 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 levels but have gonadotropins in the normal or low range.

2 DOSAGE AND ADMINISTRATION**2.1 General Dosing**

The recommended starting dose of AndroGel is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. AndroGel must not be applied to the genitals. AndroGel is supplied as either a pump or in individual packets. After applying the gel, the application site should be allowed to dry for a few minutes prior to dressing. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including AndroGel, are flammable. Hands should be washed with soap and water after AndroGel has been applied. [see Warnings and Precautions (5.2, 5.10)].

2.2 Administration**Multi-Dose Pump**

Patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. After the priming procedure, patients should completely depress the pump one time (actuation) for every 1.25 g (AndroGel Pump) of product required to achieve the daily prescribed dosage. The product may be delivered directly into the palm of the hand and then applied to the desired application sites, either one pump actuation at a time or upon completion of all pump actuations required for the daily dose. Alternatively, the product can be applied directly to the application sites. Application directly to the sites may prevent loss of product that may occur during transfer from the palm of the hand onto the application sites. Table 1 has specific dosing guidelines for adult males when the 75 g AndroGel Pump is used.

Table 1: Specific Dosing Guidelines for Using the Adult Multi-Dose Pump

Prescribed Daily Dose	Number of Pump Actuations in 75 g Pump
5 g	4 (once daily)
7.5 g	6 (once daily)
10 g	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.

2.3 Dose Adjustment and Patient Assessments

- To ensure proper dosing, serum testosterone levels should be measured at intervals and replaced to serum testosterone levels in the normal range. If the serum testosterone concentration is below the normal range, the daily AndroGel dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum testosterone concentration exceeds the normal range, the daily AndroGel dose may be decreased. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 5 g, AndroGel therapy should be discontinued.

44 The following is general advice for treating and monitoring adult patients on AndroGel. No specific recommendations can be made.

- 45 • Prescribers should be aware that testosterone is contraindicated in men with known or suspected prostate cancer. Therefore, evaluation for prostate
46 cancer prior to initiation of AndroGel therapy is appropriate [see *Contraindications (4)*].
- 47 • Based on results from controlled studies, serum PSA may rise when taking AndroGel. Therefore, periodic assessment of serum PSA is recommended in
48 patients taking AndroGel [see *Adverse Reactions (6.1)*].
- 49 • Based on results from controlled studies, worsening of BPH may occur in patients taking AndroGel [see *Adverse Reactions (6.1)*]. Therefore, periodic
50 assessments for signs and symptoms of BPH are recommended in patients taking AndroGel.
- 51 • Hematocrit, serum lipid profile, and liver function test should be monitored in patients taking AndroGel [see *Warnings and Precautions (5.9)*].

52 3 DOSAGE FORMS AND STRENGTHS

53 AndroGel (testosterone gel) 1% for topical use is available in either unit-dose packets or multiple-dose pumps. The 75 g (60 metered-dose) pump delivers
54 1.25 g of product when the pump mechanism is fully depressed once.

55 AndroGel is available in the following three package containers:

- 56 • 2 x 75 g pumps (each pump dispenses 60 metered 1.25 g doses)
- 57 • 2.5 g packet
- 58 • 5 g packet

59 4 CONTRAINDICATIONS

60 AndroGel should not be used in any of the following patients:

- 61 • 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
62 *Nonclinical Toxicology (13.1)*].
- 63 • Women who are or may become pregnant, or who are breastfeeding. AndroGel can cause fetal harm when administered to a pregnant woman. AndroGel
64 may cause serious adverse reactions in nursing infants. Exposure of a female fetus or nursing infant to androgens may result in varying degrees of
65 virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with
66 AndroGel [see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.1, 8.3)*].
- 67 • Men with known hypersensitivity to any of its ingredients, including alcohol and soy products.

68 5 WARNINGS AND PRECAUTIONS

69 5.1 Worsening of BPH and Potential Risk of Prostate Cancer

- 70 • Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH.
- 71 • Patients treated with androgens may be at increased risk for prostate cancer. Evaluation of the patient for prostate cancer prior to initiating and
72 during treatment with androgens is appropriate [see *Warnings and Precaution (5.9)*, *Adverse Reactions (6.1)*, and *Nonclinical Toxicology (13.1)*].
- 73 • Increases in serum PSA from baseline values were seen in approximately 18% of individuals in an open label study of 162 hypogonadal men
74 treated with AndroGel for up to 42 months. Most of these increases were seen within the first year of therapy [see *Contraindications (4)*, *Warnings*
75 *and Precautions (5.9)*, *Adverse Reactions (6)*, and *Nonclinical Toxicology (13.1)*].

76 5.2 Potential for Testosterone Transfer to Others

77 Transfer of testosterone to others (including women and children) can occur when vigorous skin-to-skin contact is made with the application site
78 [see *Clinical Studies (14.3)*]. The following precautions are recommended to minimize potential transfer of testosterone from AndroGel-treated skin to
79 another person:

- 80 • Patients should wash their hands immediately with soap and water after application of AndroGel.
- 81 • Patients should cover the application site(s) with clothing after the gel has dried (e.g., a shirt).
- 82 • In the event that unwashed or unclothed skin to which AndroGel has been applied does come in direct contact with the skin of another person, the
83 general area of contact on the other person should be washed with soap and water as soon as possible. In vitro studies show that residual
84 testosterone is removed from the skin surface by washing with soap and water.
- 85 • Women and children should avoid skin contact with AndroGel application sites in males. Changes in body hair distribution, significant increase in
86 acne, or other signs of virilization should be brought to the attention of a physician. AndroGel may cause fetal harm in a pregnant woman due to
87 virilization of a female fetus [see *Use in Specific Populations (8.1)*].

88 5.3 Use in Women

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

91 5.4 Potential for Adverse Effects on Spermatogenesis

92 At large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone
93 (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

94 5.5 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 is not known to produce these adverse effects.

There are rare reports of hepatocellular carcinoma in patients receiving long-term oral therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

5.6 Edema

Drugs in the androgen class 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)].

5.7 Gynecomastia

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

5.8 Sleep Apnea

The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases [see Adverse Reactions (6.2)].

5.9 Laboratory Tests

- Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Increase in red blood cell mass may increase the risk for a thromboembolic event.
- Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.
- Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.
- Androgens 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.

5.10 Flammable until Dry

- Alcohol Based Products including AndroGel are flammable; therefore avoid fire, flame or smoking until the gel 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 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 in the 180-Day Controlled Clinical Trial

Adverse Event	Dose of AndroGel		
	5 g N = 77	7.5 g N = 40	10 g 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.

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

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

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

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

141 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
142 AndroGel and reported by > 1% of patients is shown in Table 3.

143 **Table 3: Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel 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

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

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

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

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

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

154 Increases in Serum PSA Observed in Clinical Trials of Hypogonadal Men

156 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
157 6 months thereafter in the 162 hypogonadal men on AndroGel in the 3-year extension study. There was no additional statistically significant increase
158 observed in mean PSA from 6 months through 36 months. However, there were increases in serum PSA observed in approximately 18% of individual
159 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.

160 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.
161 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
162 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
163 the patients who met this criterion (23 of 29; 79%).

164 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,
165 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
166 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,
167 and Final, respectively.

168 **6.2 Postmarketing Experience**

169 The following adverse reactions have been identified during post approval use of AndroGel. Because the reactions are reported voluntarily from a
170 population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

171 Hypogonadal Men

172 Table 4 includes adverse reactions that have been identified postmarketing.

Table 4: Adverse Drug Reactions from Postmarketing Experience of AndroGel 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 GCTP, 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 levels, 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)

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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, insulin requirements.

7.2 Corticosteroids

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.

7.3 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy**

Pregnancy Category X: AndroGel is contraindicated during pregnancy or in women who may become pregnant. It is teratogenic and may cause fetal harm [see *Contraindications (4)*]. 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 is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants [see *Contraindications (4)*].

Testosterone and other androgens may adversely affect lactation.

8.4 Pediatric Use

Safety and efficacy of AndroGel in males < 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 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.

8.6 Renal or Hepatic Impairment

No formal studies were conducted involving patients with renal or hepatic insufficiencies.

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9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

Oral ingestion of AndroGel will not result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

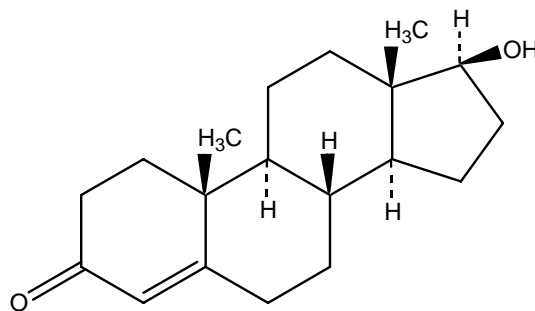
10 OVERDOSAGE

There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident. Treatment of overdosage would consist of discontinuation of AndroGel together with appropriate symptomatic and supportive care.

11 DESCRIPTION

AndroGel (testosterone gel) 1% is a clear, colorless hydroalcoholic gel containing 1% testosterone. Topical administration of AndroGel 5 g, 7.5 g, or 10 g contains 50 mg, 75 mg, or 100 mg of testosterone, respectively, is to be applied daily to the skin's surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period.

The active pharmacologic ingredient in AndroGel is testosterone. 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

Inactive ingredients in AndroGel 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 has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.3 Pharmacokinetics

Adult Males

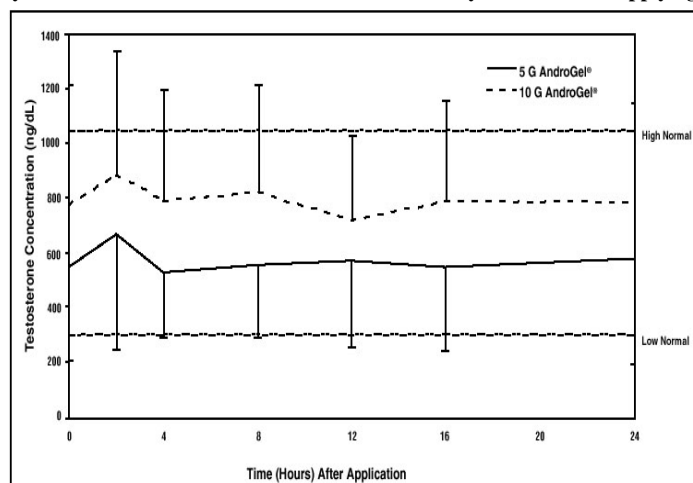
Absorption

AndroGel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (298 – 1043 ng/dL) seen in healthy men. AndroGel 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 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. Therefore, 5 g and 10 g of AndroGel systemically deliver approximately 5 mg and 10 mg of testosterone, respectively. In a study with 10 g of AndroGel, 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 level 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, 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 (<300 ng/dL) maintained on 5 g or 10 g of AndroGel for 30 days. The average (\pm SD) daily testosterone concentration produced by AndroGel 10 g on Day 30 was 792 (\pm 294) ng/dL and by AndroGel 5 g 566 (\pm 262) ng/dL.

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



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

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

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

DHT concentrations increased in parallel with testosterone concentrations during AndroGel treatment. After 180 days of treatment in adult males, mean DHT concentrations were within the normal range with 5 g AndroGel and were about 7% above the normal range after a 10 g dose. The mean steady-state DHT/T ratio during 180 days of AndroGel treatment remained within normal limits and ranged from 0.23 to 0.29 (5 g/day) and from 0.27 to 0.33 (10 g/day).

Excretion

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

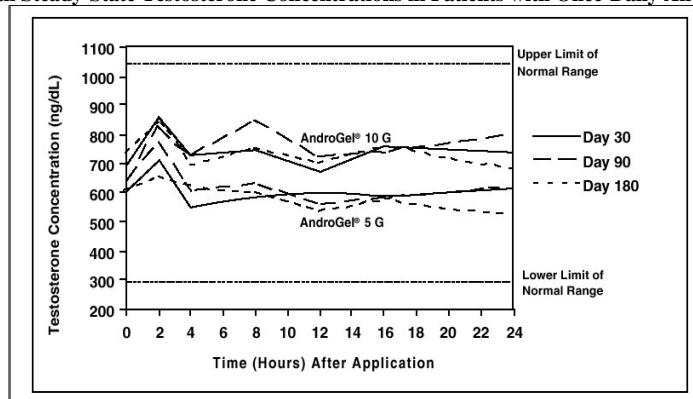
Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility 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.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Hypogonadal Males

AndroGel 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 5 g daily, 78 patients to AndroGel 10 g daily, and 76 patients to a non-scrotal testosterone transdermal system. The study was double-blind for dose of AndroGel but open-label for active control. Patients who were originally randomized to AndroGel and who had single-sample serum testosterone levels above or below the normal range on Day 60 were titrated to 7.5 g daily on Day 91. During the Extended Treatment Period (Days 91-180), 51 patients continued on AndroGel 5 g daily, 52 patients continued on AndroGel 10 g daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received AndroGel 7.5 g daily. Upon completion of the initial study, 163 enrolled and 162 patients received treatment in an open-label extension study of AndroGel 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 5 g and 10 g. In patients continuing on AndroGel 5 g and 10 g, these mean testosterone levels 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 for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed AndroGel treatment.

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

287

288 Table 5 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 5 g, 7.5 g, or 10 g of AndroGel. The 7.5 g dose
289 produced mean concentrations intermediate to those produced by 5 g and 10 g of AndroGel.

290

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

	5 g N = 44	7.5 g N = 37	10 g N = 48
Cavg	555 \pm 225	601 \pm 309	713 \pm 209
Cmax	830 \pm 347	901 \pm 471	1083 \pm 434
Cmin	371 \pm 165	406 \pm 220	485 \pm 156

291

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

293

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

296

297 AndroGel 5 g/day and 10 g/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 7.5 g dose group
298 were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with 10 g AndroGel.

299

300

301 AndroGel treatment at 5 g/day and 10 g/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,
302 increased with AndroGel treatment, as did the subjective score for "satisfactory duration of erection." AndroGel treatment at 5 g/day and 10 g/day produced
303 positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 7.5 g dose. DHT concentrations
304 increased in parallel with testosterone concentrations at AndroGel doses of 5 g/day and 10 g/day, but the DHT/T ratio stayed within the normal range,
305 indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of
306 starting treatment with AndroGel 5 or 10 g/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal
307 men. Serum levels of SHBG decreased very slightly (1 to 11%) during AndroGel treatment. In men with hypergonadotropic hypogonadism, serum levels of
308 LH and FSH fell in a dose- and time-dependent manner during treatment with AndroGel.

309

14.2 Phototoxicity in Humans

310

311 The phototoxic potential of AndroGel 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
312 (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,
313 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
314 ultraviolet light did not produce increased inflammation relative to non-irradiated sites, indicating no phototoxic effect.

315

14.3 Testosterone Transfer from Male Patients to Female Partners

316

317 The potential for dermal testosterone transfer following AndroGel use was evaluated in a clinical study between males dosed with AndroGel and their
untreated female partners. Two (2) to 12 hours after AndroGel (10 g) application by the male subjects, the couples (N = 38 couples) engaged in daily, 15-
318 minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the AndroGel application sites. Under these study
319 conditions, all unprotected female partners had a serum testosterone concentration >2 times the baseline value at some time during the study. When a shirt
320 covered the application site(s), the transfer of testosterone from the males to the female partners was completely prevented.

321

16 HOW SUPPLIED/STORAGE AND HANDLING

322

323 AndroGel is supplied in non-aerosol, metered-dose pumps. The pump is composed of plastic and stainless steel and an LDPE/aluminum foil inner liner
encased in rigid plastic with a polypropylene cap. Each 88 g AndroGel Pump in the twin package is capable of dispensing 75 g or 60 metered 1.25 g doses.

324

325 AndroGel 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 pumps (each pump dispenses 60 metered 1.25 g doses)
0051-8425-30	30 packets (2.5 g per packet)
0051-8450-30	30 packets (5 g per packet)

326 **Keep AndroGel out of the reach of children.**

327 **Storage**

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

329 **Disposal**

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

332 **17 PATIENT COUNSELING INFORMATION**

333 **See FDA-approved patient labeling (17.3)**

334 **17.1 Potential Adverse Reactions with Androgens**

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

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

341 **17.2 Instructions for Use of AndroGel**

- 342 • Patients should be informed to apply AndroGel once daily (preferably in the morning) to clean, dry skin of the shoulders and upper arms and/or
343 abdomen. To prevent transfer of AndroGel to others, patient should wash their hands after application and cover the application site with clothing.
- 344 • **Advise patients that AndroGel is an alcohol based product and is flammable, therefore avoid fire, flame or smoking until the gel has dried.**
- 345 • Counsel patients on the importance of adhering to all recommended monitoring by their healthcare professional.
- 346 • Advise patients to report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.

347 **17.3 FDA-Approved Patient Labeling**

348 AndroGel (testosterone gel) 1% CIII is available packaged with 2 x 75 g pumps (each pump dispenses 60 metered 1.25 g doses) or in a box of 30 packets
349 with 2.5g or 5g gel.

350 This is a summary of the important information about AndroGel. For details, talk to your healthcare professional and refer to the package insert.

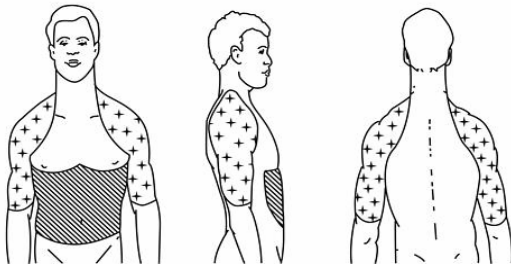
351 **1. What Disease or Condition Does AndroGel Treat?**

352 Your healthcare provider has prescribed this medication because your body does not produce enough testosterone. The medical term for this condition
353 is hypogonadism.

354 **2. How Should AndroGel (Pump or Packet) Be Applied?**

355 It is important that you use AndroGel as prescribed by your healthcare professional. If you experience serious problems, contact your healthcare
356 professional. Your healthcare professional will tell you how much AndroGel to use each day.

Men should apply gel to starred (upper arm/shoulders) or shaded (abdomen) areas only.



357
358 **Figure3: Site(s) of Gel Application**

- 359 • **AndroGel should be applied once daily at the same time each day** (preferably every morning) to clean, dry, healthy, intact skin of the
360 shoulders, upper arms and/or abdomen. If you take a bath or shower in the morning, use AndroGel **after** your bath or shower.
- 361 • AndroGel **should not** be applied to the **penis or scrotum**, or to skin with open sores, wounds or irritation.
- 362 • **Wash your hands** with soap and water immediately **after application** to reduce the chance that the medication will spread from your hands to
363 other people.
- 364 • Let AndroGel dry for a few minutes before you dress.
- 365 • **AndroGel is flammable until dry**; allow the gel to dry before smoking or going near an open flame.
- 366 • **Wait 5 to 6 hours** before showering or swimming. This will ensure that the greatest amount of AndroGel is absorbed into your system.

367 **How to use the AndroGel pump?**

368 It is important that you read and follow these directions on how to use the AndroGel Pump properly. Before using the pump for the first time, you must
369 prime the AndroGel pump by fully depressing the pump three times and discarding the gel. The unused gel should be discarded in a manner to avoid
370 accidental exposure or ingestion by household members or pets. Fully depress the pump the appropriate number of times to deliver the daily dose
371 prescribed by your healthcare provider. The product may be delivered directly into the palm of your hand and then applied to the desired application
372 sites, either one pump depression at a time or upon completion of all pump depressions required for the daily dose.

373 **How to use the AndroGel packets?**

374 Open one AndroGel aluminum foil packet by folding the top edge at the perforation and tearing completely across the packet along the perforation.
375 Squeeze the contents into the palm of your hand. Squeeze from the bottom of the packet toward the top. If you like, you may squeeze a portion of the
376 gel from the packet into the palm of your hand and apply to application site(s). Repeat until the entire contents of the packet have been applied.

377 **3. What Should You Discuss With Your Healthcare Professional?**

378 **Before you start using AndroGel, tell your healthcare professional if you:**

- 379 • Have prostate cancer or breast cancer.
- 380 • Have a known hypersensitivity to any of AndroGel's components, including individuals who are hypersensitive to testosterone that is chemically
381 synthesized from soy.

382 **4. What Other Drugs Should Not Be Used Together With AndroGel?**

383 Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins and herbal
384 supplements. AndroGel can affect how your body handles other drugs. Changes in your dose or careful monitoring may be needed if you are taking any
385 of the following medications:

- 386 • Insulin
- 387 • Corticosteroids
- 388 • Oral Anticoagulants

389 **5. What Are The Side Effects And Risks?**

390 **Possible side effects of AndroGel** to discuss with your healthcare professional include:

391 **Most common:** Skin irritation where gel is applied, breast development or tenderness, acne, prostate enlargement, changes in lab test results
392 and changes in urinary habits.

393 **Contact your healthcare professional** if you experience any of the following adverse reactions:

- 394 • Too frequent or persistent erections of the penis.
- 395 • Any nausea, vomiting, changes in skin color or ankle swelling.
- 396 • Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- 397 • Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the
398 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
399 flow.

400 **The major risks of AndroGel** include:

401 **Prostate Disorders:** Patients treated with testosterone may be at an increased risk for prostate enlargement, and prostate cancer. Talk to your
402 healthcare provider for more information on risk factors and ways to monitor for prostate disorders.

403 **Testosterone Transfer:** Transfer of testosterone to others (including women and children) can occur when vigorous skin-to-skin contact is made with
404 the application site. AndroGel must not be used by women, and exposure to the active ingredient testosterone in pregnancy can cause fetal harm.
405 Notify your healthcare provider if your female partner develops changes in hair distribution, increases in acne or other signs of masculinity.

406 **6. How Should AndroGel Be Stored?**

407 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep out of the reach of children.

408 **7. Is There Anything Else I Need To Know When Using AndroGel?**

409 Your healthcare professional has prescribed AndroGel to meet your specific needs; never share your AndroGel with anyone. If you have any questions
410 or concerns about your AndroGel treatment, ask your healthcare provider or pharmacist.

411
412
413 **Manufactured By:**

414 Laboratoires Besins International
415 Montrouge, France

416 **For:**

417 Unimed Pharmaceuticals, LLC
418 A Solvay Pharmaceuticals, Inc. Company
419 Marietta, GA 30062-2224

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