DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-015/S-011

Solvay Pharmaceuticals, Inc.
Attention: Steven Wojtanowski, R.Ph., M.P.H.
Assistant Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Wojtanowski

Please refer to your supplemental new drug application dated May 20, 2004, received July 1, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1%.

We acknowledge receipt of your submissions dated June 16 and July 19, 2005.

Your submission of June 16, 2005 constituted a complete response to our April 29, 2005 action letter.

This supplemental new drug application proposes changes to your approved product labeling based on an open-label long-term extension study (UMD-98-035) entitled, "*A Long-Term Study of the Safety and Effectiveness of Testosterone-Gel for Hormonal Replacement in Hypogonadal Men.*"

We completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-015/S-011**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit your proposed draft labeling for the patient package insert to reflect the revisions to the package insert.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Agreed-upon package insert

℞ only

AndroGel® (testosterone gel) 1% CIII

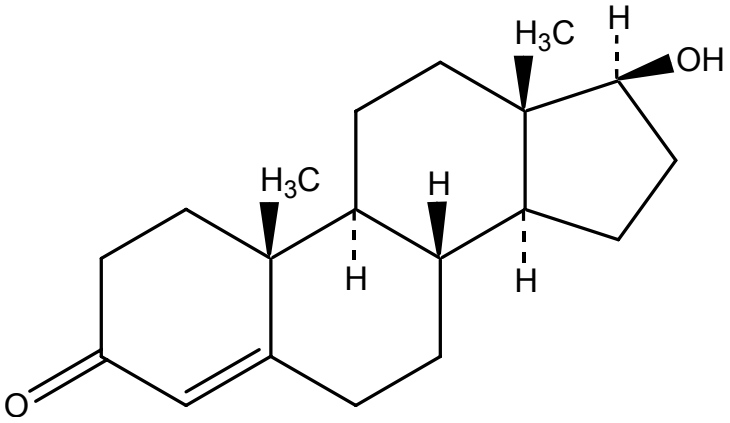
500122/500127
Rev Aug 2005

DESCRIPTION

AndroGel® (testosterone gel) 1% is a clear, colorless hydroalcoholic gel containing 1% testosterone. AndroGel provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

A daily application of AndroGel 5 g, 7.5 g, or 10 g contains 50 mg, 75 mg, or 100 mg of testosterone, respectively, 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.



Testosterone

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

Inactive ingredients in AndroGel are ethanol 67.0%, purified water, sodium hydroxide, carbomer 980 and isopropyl myristate; these ingredients are not pharmacologically active.

CLINICAL PHARMACOLOGY

AndroGel (testosterone gel) delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (298 – 1043 ng/dL) seen in healthy men.

Testosterone – General Androgen Effects:

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. Symptoms associated with male hypogonadism include impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis. Hypogonadism is a risk factor for osteoporosis in men.

Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

There is a lack of substantial evidence that androgens are effective in accelerating fracture healing or in shortening postsurgical convalescence.

Pharmacokinetics

Absorption: 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 (± SD) daily testosterone concentration produced by AndroGel 10 g on Day 30 was 792 (± 294) ng/dL and by AndroGel 5 g 566 (± 262) ng/dL.

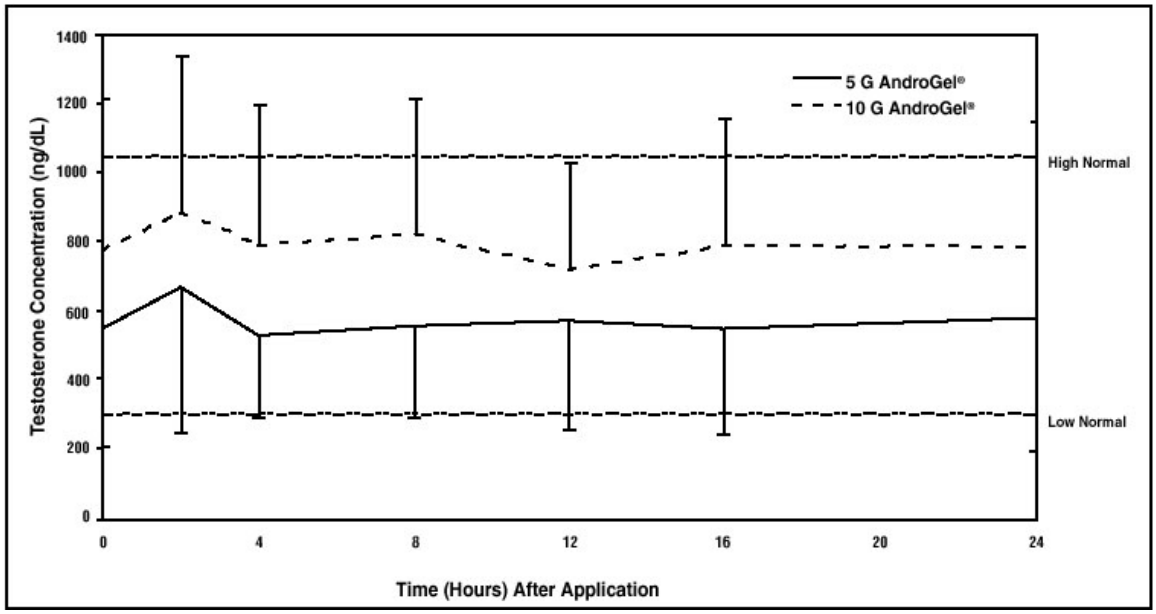


FIGURE 1: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying AndroGel Once Daily

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 chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen. SHBG-binding capacity is high in prepubertal children, declines during puberty and adulthood, and increases again during the later decades of life. 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 binds with greater affinity to SHBG than does testosterone. In many tissues, the activity of testosterone depends on its reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action. In reproductive tissues, DHT is further metabolized to 3-α and 3-β androstanediol.

DHT concentrations increased in parallel with testosterone concentrations during AndroGel treatment. After 180 days of treatment, 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 (as determined by the analytical laboratory involved with this clinical trial) 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.

***Special Populations*:** In patients treated with AndroGel, there are no observed differences in the average daily serum testosterone concentration at steady state based on age, cause of hypogonadism or body mass index. No formal studies were conducted involving patients with renal or hepatic insufficiencies.

Clinical Studies

AndroGel was evaluated in a multicenter, 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.

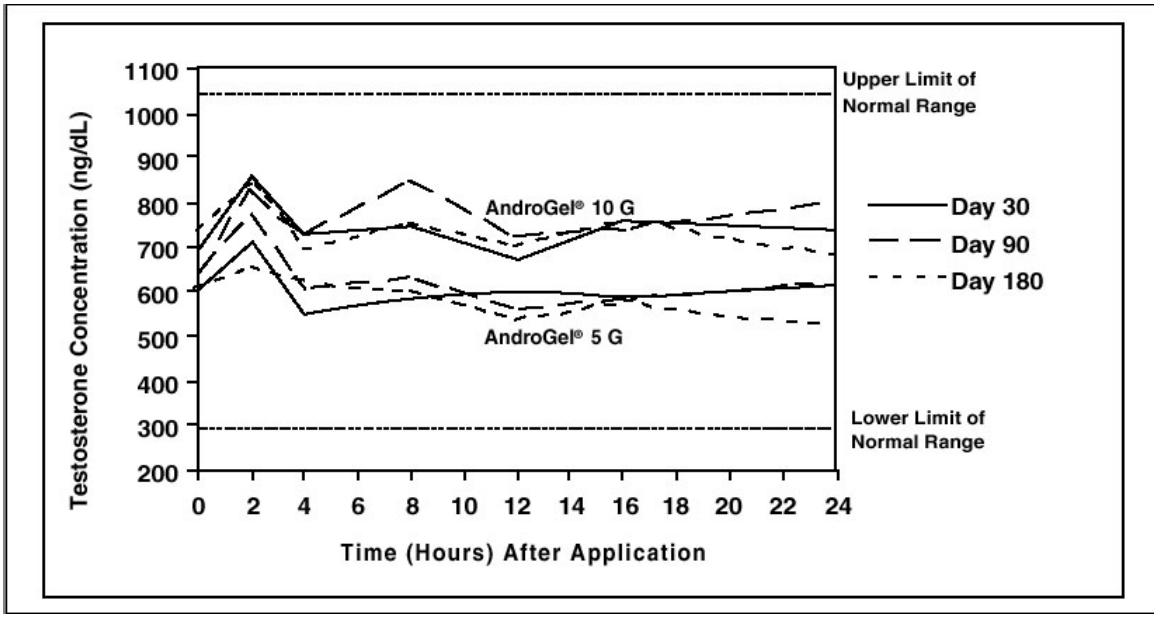


FIGURE 2: Mean Steady-State Testosterone Concentrations in Patients with Once-Daily AndroGel Therapy

Table 1 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 produced mean concentrations intermediate to those produced by 5 g and 10 g of AndroGel.

TABLE 1: Mean (± 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 ± 225	601 ± 309	713 ± 209
Cmax	830 ± 347	901 ± 471	1083 ± 434
Cmin	371 ± 165	406 ± 220	485 ± 156

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.

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 were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with 10 g AndroGel.

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, 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 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 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, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with AndroGel 5 or 10 g/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 treatment. In men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and time-dependent manner during treatment with AndroGel.

***Potential for Phototoxicity*:** 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 (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 2-5. 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.

Potential for Testosterone Transfer: 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 to 12 hours after AndroGel (10 g) application 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 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.

INDICATIONS AND USAGE

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

1. 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.
2. 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.

AndroGel has not been clinically evaluated in males under 18 years of age.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

AndroGel is not indicated for use in women, has not been evaluated in women, and must not be used in women.

Pregnant women should avoid skin contact with AndroGel application sites in men. Testosterone may cause fetal harm. In the event that unwashed or unclothed skin to which AndroGel has been applied does come in direct contact with the skin of a pregnant woman, the general area of contact on the woman should be washed with soap and water as soon as possible. *In vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.

AndroGel should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone USP that is chemically synthesized from soy.

WARNINGS

1. 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 testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. AndroGel is not known to produce these adverse effects.
2. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.
3. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men. Increases in serum PSA from baseline values were seen in approximately 18% of individuals in an open label study of 162 hypogonadal men treated with AndroGel for up to 42 months. Most of these increases were seen within the first year of therapy. (see **ADVERSE REACTIONS** and **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** and **Laboratory Tests**).
4. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.
5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.
6. The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.
7. ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.

PRECAUTIONS

Transfer of testosterone to another person can occur when vigorous skin-to-skin contact is made with the application site (see **Clinical Studies**). The following precautions are recommended to minimize potential transfer of testosterone from AndroGel-treated skin to another person:

- Patients should wash their hands immediately with soap and water after application of AndroGel.
- Patients should cover the application site(s) with clothing after the gel has dried (e.g. a shirt).

- 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 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 testosterone is removed from the skin surface by washing with soap and water.

Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.

General

The physician should instruct patients to report any of the following:

- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin color, or ankle swelling.
- Breathing disturbances, including those associated with sleep.

Information for Patients

Advise patients to carefully read the information brochure that accompanies each carton of 30 AndroGel single-use packets or 75 g AndroGel Pump.

Advise patients of the following:

- AndroGel should not be applied to the scrotum.
- AndroGel should be applied once daily to clean dry skin.
- After application of AndroGel, it is currently unknown for how long showering or swimming should be delayed. For optimal absorption of testosterone, it appears reasonable to wait at least 5-6 hours after application prior to showering or swimming. Nevertheless, showering or swimming after just 1 hour should have a minimal effect on the amount of AndroGel absorbed if done very infrequently.
- SINCE ALCOHOL BASED GELS ARE FLAMMABLE, AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.

Laboratory Tests

1. Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy.
2. Liver function, prostatic specific antigen, cholesterol, and high-density lipoprotein should be checked periodically.
3. To ensure proper dosing, serum testosterone concentrations should be measured (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Propranolol: In a published pharmacokinetic study of an injectable testosterone product, administration of testosterone cypionate led to an increased clearance of propranolol in the majority of men tested.

Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus, these drugs should be administered cautiously, particularly in patients with cardiac or hepatic disease.

Drug/Laboratory Test Interactions

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Data: 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.

Human Data: 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.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy.

In men receiving testosterone replacement therapy, screening for prostate cancer should be consistent with current practices for eugonadal men. Increases in serum PSA from baseline values were reported in approximately 18% of individual patients treated for up to 42 months in an open-label safety study (see **ADVERSE REACTIONS**).

Pregnancy Category X (see **CONTRAINDICATIONS**) – Teratogenic Effects: AndroGel is not indicated for women and must not be used in women.

Nursing Mothers: AndroGel is not indicated for women and must not be used in women.

Pediatric Use: Safety and efficacy of AndroGel in pediatric patients have not been established.

ADVERSE REACTIONS

In a controlled clinical study, 154 patients were treated with AndroGel for up to 6 months (see **Clinical Studies**). Adverse Events possibly, probably or definitely related to the use of AndroGel and reported by ≥1% of the patients are listed in Table 2.

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: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine, or elevated total bilirubin.

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

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

The following adverse events possibly related to the use of AndroGel occurred in fewer than 1% of patients: amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

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

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

In an uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with AndroGel; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other. Among 17 patients in foreign clinical studies there was one instance each of acne, erythema and benign prostate adenoma associated with a 2.5% testosterone gel formulation applied dermally.

One hundred sixty-two (162) patients received AndroGel for up to 3 years in a long-term follow-up study for patients who completed the controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or definitely related to the use of AndroGel and reported by 2 or more subjects in at least one treatment group.

TABLE 3: Incidence of Treatment-Emergent Adverse Events Possibly, Probably or Definitely Related to the Use of AndroGel in the 3 Year Open-Label Extension Clinical Trial

Adverse Event Category/Classification	Treatment Group % (N = 162)
Lab Test Abnormal[+]	9.3% (15)
Skin dry	1.9% (3)
Application Site Reaction	5.6% (9)
Acne	3.1% (5)
Pruritus	1.9% (3)
Enlarged Prostate	11.7% (19)
Carcinoma of Prostate	1.2% (2)
Urinary Symptoms*	3.7% (6)
Testis Disorder**	1.9% (3)
Gynecomastia	2.5% (4)
Anemia	2.5% (4)

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

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

** *Testis disorder* included three patients. There were two patients with a non-palpable testis and one patient 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). Nine patients discontinued treatment due to adverse events possibly related to treatment with AndroGel, including 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). All patients who discontinued due to an increase in serum PSA did so by Day 357.

Increases in Serum PSA

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. While there was no statistically significant increase in mean PSA from 6 months through 36 months of AndroGel treatment for the overall group of 162 patients enrolled in the long-term extension study, there were increases in serum PSA seen in approximately 18% of individual patients. In the long-term

extension study, the overall mean change from baseline in serum PSA values for the entire group was 0.11 ng/mL.

Twenty-nine (29) (18%) patients met the per-protocol criterion for increase in serum PSA value, defined as a value ≥2X the baseline value or any single absolute value ≥6 ng/mL. Twenty-five of these patients met this criterion by virtue of a post-baseline value at least twice the baseline value. In most of these cases (22/25), the maximum serum PSA value attained was ≤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 AndroGel-treated patients). In two of these AndroGel-treated 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.

DRUG ABUSE AND DEPENDENCE

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.

OVERDOSAGE

No reports of AndroGel overdose have been received. However, there is one report of acute overdosage by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

DOSAGE AND ADMINISTRATION

The recommended starting dose of AndroGel is 5 g delivering 5 mg of testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper dosing. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily AndroGel dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g as instructed by the physician.

AndroGel is available in either unit-dose packets or multiple-dose pumps. The metered-dose pump delivers 1.25 g of product when the pump mechanism is fully depressed once.

AndroGel must not be applied to the genitals.

If using the multi-dose AndroGel 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 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. Please refer to the chart below for specific dosing guidelines when the AndroGel Pump is used.

Prescribed Daily Dose	Number of Pump Actuations
5 g	4 (once daily)
7.5 g	6 (once daily)
10 g	8 (once daily)

If using the 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.

Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after AndroGel has been applied.

HOW SUPPLIED

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

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 individual packaged AndroGel Pump is capable of dispensing 75 g or 60 metered 1.25 g doses.

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)

Keep AndroGel out of the reach of children.

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 pumps or used AndroGel packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets. In addition, any discarded gel should be thoroughly rinsed down the sink or discarded in the household trash in a manner that prevents accidental application or ingestion by children or pets.

Manufactured by:

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