8551 '01 JUL 13 P1:36

July 3, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services, Rm. 1-23
12420 Parklawn Dr.
Rockville, MD 20857

Attention: Gregory Davis, RPh, Branch Chief,
Review Support Branch Division of Labeling and Program Support, Office of Generic Drugs

Dear Mr. Davis,

Enclosed please find four copies of the ANDA Suitability Petition which TestoCreme®, LLC, submits under section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act. This petition includes the actual Citizen Petition outlining our request, along with a copy of side-by-side labels for Testocreme® 5% (testosterone gel) and AndroGel® 1% (testosterone gel), the reference listed drug.

Both TestoCreme and AndroGel contain the same active ingredient, testosterone, USP. While we are requesting permission to submit an ANDA for a drug product with a different strength of testosterone, this change should not impact safety or efficacy, since patients would be directed to apply the same absolute amount of testosterone each day. Thus, TestoCreme can be anticipated to have the same therapeutic effect as the reference listed drug, when administered to patients (according to the Dosage and Administration section of the proposed label) for each condition of use listed in the approved labeling for AndroGel.

Should you have any questions or require additional information in order to process this petition, please contact Margie Nemcik-Cruz, Regulatory Consultant to the TestoCreme project, by phone or fax at (650) 494-1177.

Sincerely,

Abraham H. Kryger, DMD, MD
CEO, TestoCreme®, LLC

01P.0302

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Testocreme, LLC 1084 Cass Street, Monterey, CA 93940 Phone: (831) 373 - 4406 Fax: (831) 373 - 4481

TestoCreme® 5% (testosterone gel)
ANDA Suitability Petition

July 10, 2001
Original

July 10, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services, Rm. 1-23
12420 Parklawn Dr.
Rockville, MD 208573

Citizen Petition

The undersigned submits this petition under 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of Food and Drugs to approve a suitability petition for the submission of an Abbreviated New Drug Application for a generic that differs in strength from the reference listed drug.

A. Action requested

TestoCreme®, LLC, hereby requests that the Commissioner of Food and Drugs approve this suitability petition to allow the submission of an ANDA for TestoCreme® 5% (testosterone gel), based on a determination of bioequivalence to AndroGel® 1% (testosterone gel), the relevant reference listed drug. Both of these products contain the same active ingredient, testosterone, USP.

B. Statement of grounds

Testocreme®, LLC, the sponsor, requests approval of an ANDA suitability petition for TestoCreme® 5% (testosterone gel). The proposed label strength for this product differs from the reference listed drug, AndroGel® 1% (testosterone gel), however, the sponsor believes that a bioequivalent dose of testosterone can be delivered by topical application of a smaller volume of gel containing a higher concentration of the active without adversely impacting efficacy or safety.

B.1 Rationale for Equivalent Therapeutic Effect

Clinical pharmacology studies indicate that approximately 10 mg of testosterone are produced daily by the testes in normal men.[1,2,3] According to the approved labeling for AndroGel 1%, approximately 10% of a topically applied dose of testosterone is absorbed into the systemic circulation. Thus, AndroGel 1% is approved for daily topical application in hypogonadal men at doses between 5 g and 10 g (containing 50 to 100 mg testosterone), with the aim of delivering 5 to 10 mg of testosterone to the systemic circulation. The sponsor believes that topical application of one to two grams of TestoCreme 5% (containing 50 to 100 mg T) will lead to bioequivalent absorption of testosterone when compared to the approved dosing regimen for AndroGel 1%. In both cases the same absolute amount of testosterone is applied to the skin, what differs is the amount of gel applied. Thus, the requested change in the strength of the drug product should not impact safety. In addition, TestoCreme can be anticipated to have the same therapeutic effect as AndroGel, the reference listed drug, when administered to patients (according to the Dosage and Administration section of the proposed label) for each condition of use listed in the approved labeling for AndroGel.

B.2 Grounds for Selecting Strength of TestoCreme

A pilot study comparing the absorption of TestoCreme 5% to AndroGel 1% is being carried out by the sponsor. In this study, equivalent doses of testosterone are applied to the skin of patients. It is anticipated that approximately 6 patients will be treated in each group. While the results of this study are still being compiled, preliminary results suggest that the rate and extent of topical absorption of 2 g TestoCreme 5% is similar to that of 10 g AndroGel 1%. The sponsor, therefore, requests approval of this suitability petition with the aim of conducting a definitive

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[1] Santen RJ. The testes. In: Felig P, Baxter J, Frohman L, eds. Endocrinology and Metabolism. New York: McGraw-Hill, 1995: 885.

[2] Nankin HR, Calkins JH. Decreased bioavailable testosterone in aging normal and impotent men. J Clin Endocrinol Metab. 1986;63:1418.

bioequivalence study comparing these two products in order to submit an ANDA for TestoCreme® 5% (testosterone gel).

B.3 Safety of the Formulation

A listing of the ingredients contained in TestoCreme can be found in Table 1. All of these ingredients meet either USP or NF requirements. The natural soybean-based carrier (lecithin/isopropyl palmitate solution) found in this formulation has been used by compounding pharmacists for decades and has proven safe and non-irritating. This carrier makes it possible to formulate higher doses of testosterone in a smaller volume of gel, thus requiring exposure of a smaller body surface area to the drug. An area of skin approximately 4" in diameter on the back or the sides of the body is required for application of TestoCreme. In contrast, due to the large volume of AndroGel required to deliver the desired dose of testosterone, the entire upper torso, including the back, chest, and both shoulders and arms, needs to be used. Thus, TestoCreme should be safe for daily application in hypogonadal men at doses of 1-2 g, and the reduced body area exposed to the drug should decrease the risk of transference of drug to the patient's partner.

Table 1: Qualitative composition of TestoCreme® 5% (testosterone gel)

Component	Function	Specification
Testosterone	Active ingredient	USP
Alpha tocopherol acetate	Anti-oxidant	USP
Butylated hydroxytoluene	Anti-oxidant	NF
Edetate disodium (EDTA)	Chelating agent	USP
Ethoxy diglycol	Solvent	Reagent
Ethyl alcohol, 200 proof	Solvent	USP
Hydrochloric acid	Buffer	NF
Isopropyl palmitate	Emulsifying agent	NF
Lecithin soya, granular	Emulsifying agent	NF
Methyl paraben	Preservative	NF
Poloxamer 407 (Pluronic F127)	Surfactant	NF
Polysorbate 80	Surfactant, Emulsifying agent	NF
Potassium sorbate	Preservative	NF
Propyl paraben	Preservative	NF
Propylene glycol	Humectant, solvent	USP
Sodium hydroxide	Buffer	NF
Sorbic acid	Preservative	NF
Water, purified	Solvent	USP

B.4 Reproducibility of the Dose Delivered

The dose delivered by actuating the metered dose dispenser is both accurate and reproducible. The metered dose volume is defined by the dose chamber between the piston and spring support. With each stroke a metered volume of 0.5 mL of product is taken out of the dose chamber and at the same time filled in from the bottom of the container for the next stroke of the same amount.

Dose volume tolerances as characterized using distilled water are +/- 7.5% mean, and +/- 15% on individual strokes. Dose volume tolerance can be influenced by the physical properties of the formulation (e.g. surface tension, and viscosity). To insure that this system meets acceptable product performance standards, a dose volume tolerance study using a placebo formulation of TestoCreme will be conducted by the manufacturer of the proposed commercial dispenser.

C. Environmental impact

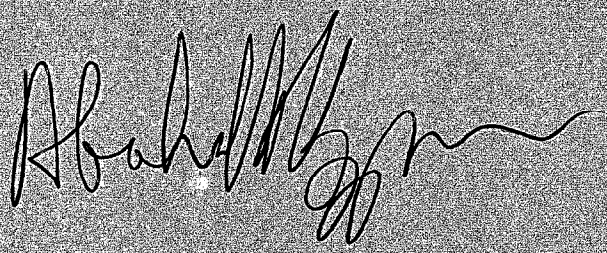
In accordance with 21 CFR 25.31 (g), TestoCreme, LLC, hereby claims a categorical exclusion to the environmental assessment requirements. The categorical exclusion claim is based on the fact that the sponsor intends to establish the bioequivalence of a generic version of a human drug product to the reference listed drug.

D. Economic impact

Not applicable.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

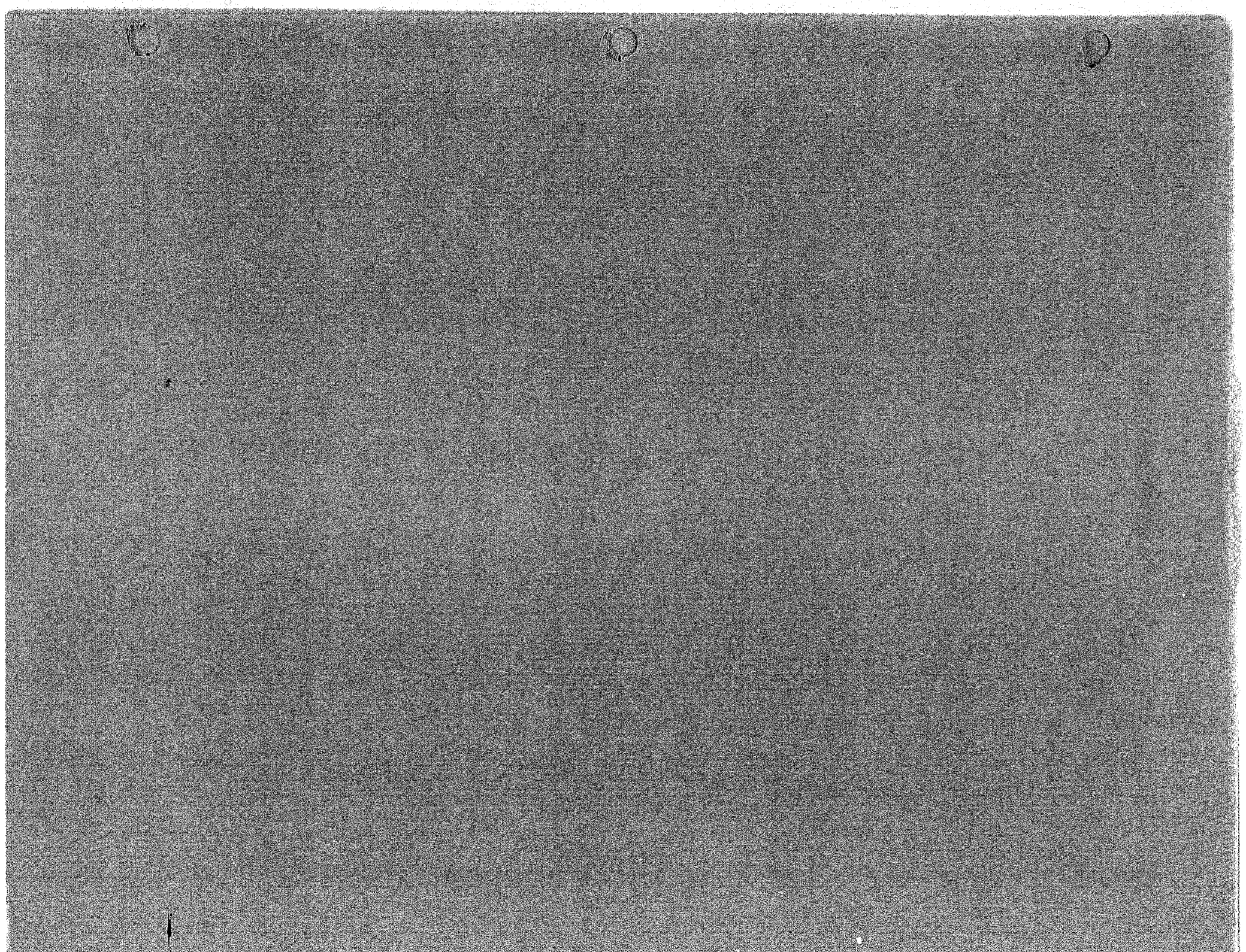
(Signature) 

(Name of petitioner) Abraham H. Kryger, DMD, MD,
CEO, TestoCreme®, LLC

(Mailing address) 1084 Cass Street
Monterey, CA 93940

(Telephone number) 831-373-4406

(Fax Number) 831-373-4481



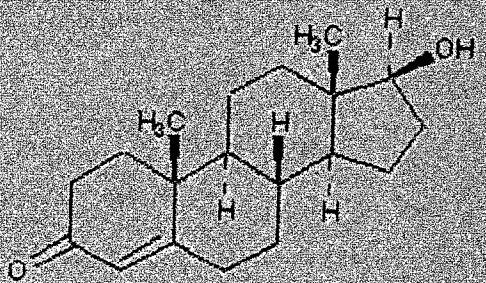
TestoCreme® Draft label	Approved AndroGel® Label

TestoCreme® 5%
(testosterone) Gel C III
DESCRIPTION

TestoCreme® (testosterone gel) is a clear, colorless organogel containing 5% testosterone. TestoCreme 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 TestoCreme 5% 1 G, 1.5 G, or 2 G delivers 50 mg, 75 mg, or 100 mg of testosterone, respectively, per day, 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 TestoCreme 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

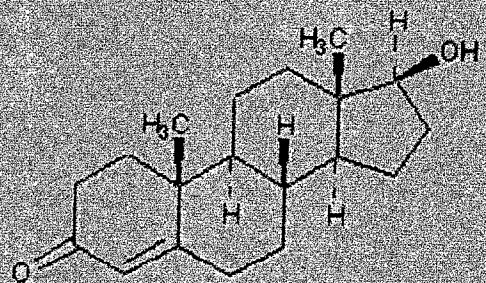
Inactive ingredients in TestoCreme are purified water, ethyl alcohol, isopropyl palmitate, soy lecithin, poloxamer 407, butylated hydroxytoluene, propylene glycol, ethoxy diglycol, disodium edetate, alpha tocopherol acetate, methyl paraben, propyl paraben, polysorbate 80, sorbic acid, potassium sorbate, hydrochloric acid, sodium hydroxide; these

AndroGel® 1%
(testosterone gel) C III
DESCRIPTION

AndroGel® (testosterone gel) 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 delivers 50 mg, 75 mg, or 100 mg of testosterone, respectively, per day, 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 68.9%, purified water, sodium hydroxide, Carbomer 940 and isopropyl myristate; these ingredients are not pharmacologically active.

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CLINICAL PHARMACOLOGY

TestoCreme® (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

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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 post-surgical convalescence. **Pharmacokinetics** Absorption TestoCreme® is an organogel 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. In a study with the 2 G dose of the 5% gel (to deliver 100 mg testosterone), 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 TestoCreme, 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 patients maintained on 5 G or 10 G of AndroGel® (to deliver 50 or 100 mg of testosterone, respectively) 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.	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 post-surgical 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. In a study with the 10 G dose (to deliver 100 mg testosterone), 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 patients maintained on 5 G or 10 G of AndroGel® (to deliver 50 or 100 mg of testosterone, respectively) 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

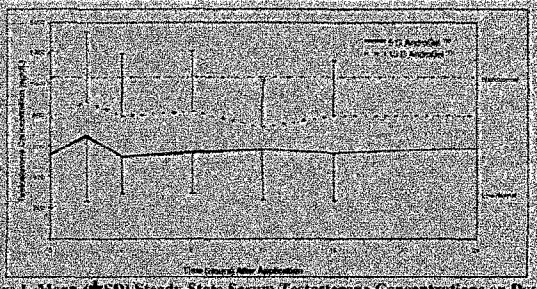
When TestoCreme® treatment is discontinued after achieving steady state, serum testosterone levels remain in the normal range for 24 to 48 hours but return to their pretreatment levels by the fifth day after the last application.

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 ten 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-αand 3-β



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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 TestoCreme®, 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® 1% 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 G daily (to deliver 50 mg testosterone), 78 patients to AndroGel® 10 G daily (to deliver 100 mg testosterone), and 76 patients to a non-scrotal testosterone transdermal system (5 mg daily). 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 (to deliver 75 mg testosterone) 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

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testosterone transdermal system (5 mg daily), and 40 patients received AndroGel® 7.5 G daily.

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 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.

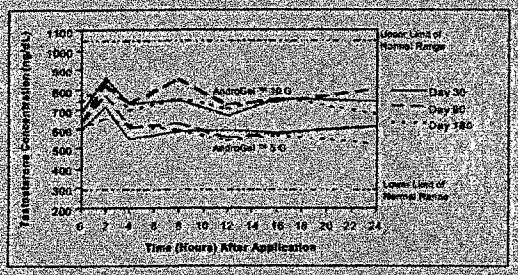


Figure 2. Mean Steady-State Testosterone Concentrations in Patients with Once-Daily AndroGel™ Therapy

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)

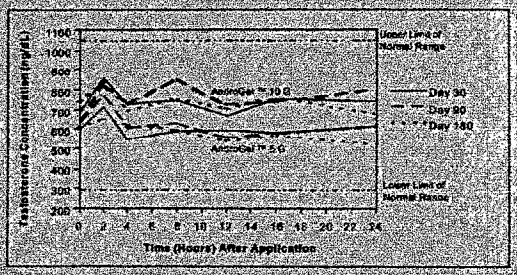
	5 G N = 44	7.5 G N = 37	10 G N = 48
Cavg	555 ± 225	601 ± 309	713 ± 209
Cmax	830 ± 347	901 ± 471	1083 ± 434
Cmin	371 ± 165	406 ± 220	485 ± 156

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

testosterone transdermal system (5 mg daily), and 40 patients received AndroGel® 7.5 G daily.

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 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.



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AndroGel® 5 G/day and 10 G/day resulted in significant increases over time in total body

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.	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 TestoCreme® 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. TestoCreme has not been clinically evaluated in males under 18 years of age.	**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. TestoCreme 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 TestoCreme application sites in men. Testosterone may cause fetal harm. In the event that unwashed or unclothed skin to which TestoCreme 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.	**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.

TestoCreme® should not be used in patients with known hypersensitivity to any of its ingredients.	AndroGel® should not be used in patients with known hypersensitivity to any of its ingredients.
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 hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis 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. Testosterone 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 (see PRECAUTIONS: Carcinogensis, Mutagensis, 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.	**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 hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatalcomplication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone 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 (see PRECAUTIONS: Carcinogensis, Mutagensis, 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.
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	**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 TestoCreme®-treated skin to another person: •Patients should wash their hands immediately with soap and water after application of TestoCreme. •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 TestoCreme 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 TestoCreme dispenser. Advise patients of the following: •TestoCreme should not be applied to the scrotum. •TestoCreme should be applied once daily to clean dry skin. •After application of TestoCreme, 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 TestoCreme absorbed if done very infrequently. Laboratory Tests 1. Hemoglobin and hematocrit levels should be	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. 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. 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	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, surveillance for prostate cancer should be consistent with current practices for eugonadal men.
Pregnancy Category X (see Contraindications)--Teratogenic Effects:
TestoCreme® is not indicated for women and must not be used in women. Nursing Mothers: TestoCreme is not indicated for women and must not be used in women.
Pediatric Use: Safety and efficacy of TestoCreme 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 Controlled Clinical Trial

Adverse Event	5 G	7.5 G	10 G
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

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ADVERSE REACTIONS

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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. 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 occasionally 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 1 instance each of acne, erythema and benign prostate adenoma associated with a 2.5% testosterone gel formulation applied dermally. One hundred six (106) patients have received AndroGel® for up to 12 months in a long-term follow-up study for patients who completed the controlled clinical trial. The preliminary safety results from this study are consistent with those reported for the controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or definitely related to the use of AndroGel® and reported by at least 1% of the total number of patients during long-term exposure to AndroGel®.	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. 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 occasionally 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 1 instance each of acne, erythema and benign prostate adenoma associated with a 2.5% testosterone gel formulation applied dermally. One hundred six (106) patients have received AndroGel® for up to 12 months in a long-term follow-up study for patients who completed the controlled clinical trial. The preliminary safety results from this study are consistent with those reported for the controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or definitely related to the use of AndroGel® and reported by at least 1% of the total number of patients during long-term exposure to AndroGel®.

Table 3. Incidence of Adverse Events Possibly, Probably or Definitely Related to the Use of AndroGel™ in the Long-Term, Follow-up Study

Adverse Event	5 G	7.5 G	10 G
Lab Test Abnormal*	4.2%	0.0%	6.3%
Peripheral Edema	1.4%	0.0%	3.1%
Acne	2.8%	0.0%	12.5%
Application Site Reaction	9.7%	10.0%	3.1%
Prostate Disorder**	2.8%	5.0%	18.8%
Urination Impaired	2.8%	0.0%	0.0%

* *Lab test abnormal* included one patient each with elevated GGTP, elevated hematocrit and hemoglobin, increased total bilirubin, worsened hyperlipidemia, decreased HDL, and hypokalemia.

***Prostate disorders* included enlarged prostate, elevated PSA results, and in one patient, a new diagnosis of prostate cancer; three patients (one taking 7.5 G daily and two taking 10 G daily) discontinued AndroGel® treatment during the long-term study because of such disorders.

DRUG ABUSE AND DEPENDENCE.

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

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

OVERDOSAGE

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 TestoCreme® 5% is 1 G (to deliver 50 mg of testosterone) applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. The cap of the metered dose dispenser should be depressed and the delivered gel should immediately be applied to the application sites.

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

Do not apply TestoCreme to the genitals.

Table 3. Incidence of Adverse Events Possibly, Probably or Definitely Related to the Use of AndroGel™ in the Long-Term, Follow-up Study

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Application Site Reaction	9.7%	10.0%	3.1%
Prostate Disorder**	2.8%	5.0%	18.8%
Urination Impaired	2.8%	0.0%	0.0%

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DOSAGE AND ADMINISTRATION

The recommended starting dose of AndroGel® 1% is 5 G (to deliver 50 mg of testosterone) applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites.

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.

Do not apply AndroGel® to the genitals.

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 TestoCreme 5% dose may be increased from 1 G to 1.5 G and from 1.5 G to 2 G as instructed by the physician.	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® 1% dose may be increased from 5 G to 7.5 G and from 7.5 G to 10 G as instructed by the physician.
HOW SUPPLIED TestoCreme® contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act. TestoCreme® is supplied in a metered dose dispenser containing 30 g of 5% TestoCreme gel. Each actuation of the metered dose dispenser delivers 0.5 G of gel to deliver 50 mg of testosterone, and is supplied as follows: NDC Number / Strength / Package Size XXXX-XXXX-XX / 5% (50mg/G) / 30 G bottle. 0.5 G gel per actuation	**HOW SUPPLIED** AndroGel® contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act. AndroGel® is supplied in unit-dose aluminum foil packets in cartons of 30. Each packet contains 2.5 G or 5.0 G of gel to deliver 25 mg or 50 mg of testosterone, respectively, and is supplied as follows: NDC Number / Strength / Package Size 0051-8425-30 / 1% (25 mg) / 30 packets. 2.5 G per packet 0051-8450-30 / 1% (50 mg) / 30 packets. 5 G per packet
Storage Store at controlled room temperature 20-25 °C (68-77 °F) [see USP].	Storage Store at controlled room temperature 20-25 °C (68-77 o F) [see USP].
Disposal Used TestoCreme® dispensers should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.	Disposal Used AndroGel® packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.
R_x Only Manufactured by: TBD For: TestoCreme®, LLC Monterey, CA 93940, USA	Rx Only Manufactured by: Laboratoires Besins Iscovesco Montrouge, France For: Unimed Pharmaceuticals, Inc. Buffalo Grove, IL 60089-1864, USA

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City Palo Alto State CA ZIP 94306

2 Your Internal Billing Reference

3 To Attn: Lt. Greg Davis, RTK

Recipient's Name Dockets Management Branch Phone 301 827-5710

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Dept. Health + Human Services

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8293 3790 8425

4a Express Package Service — Packages up to 150 lbs.

Delivery commitment may be later in some areas.

1 FedEx Priority Overnight — Next business morning

5 FedEx Standard Overnight — Next business afternoon

6 FedEx First Overnight — Earliest next business morning delivery to select locations

2 FedEx 2Day — Second business day

20 FedEx Express Saver — Third business day

77 NEW FedEx Extra Hours — Later drop-off than FedEx 2Day, morning delivery to select locations

FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service — Packages over 150 lbs.

Delivery commitment may be later in some areas.

7 FedEx 1Day Freight* — Next business day

8 FedEx 2Day Freight — Second business day

83 FedEx 3Day Freight — Third business day

* Call for confirmation.

5 Packaging — Declared value limit $500

6 FedEx Envelope*

2 FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak

Other Pkg — Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling — Include FedEx address in Section 3.

3 SATURDAY Delivery — Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes

33 SUNDAY Delivery — Available for FedEx Priority Overnight to select ZIP codes

1 HOLD Weekday at FedEx Location — Not available with FedEx First Overnight

31 HOLD Saturday at FedEx Location — Available only for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

No

4 Yes — As per attached Shipper's Declaration

6 Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg

Cargo Aircraft Only

Dangerous Goods (incl. Dry Ice) cannot be shipped in FedEx packaging or by FedEx Extra Hours service.

7 Payment Bill to:

1 Sender — Acct. No. in Section 1 will be billed

2 Recipient

3 Third Party

4 Credit Card

5 Cash/Check

FedEx Acct. No. or Credit Card No.

Exp. Date

Obtain Recip. Acct. No.

Total Packages 1

Total Weight 2

Total Charges n/a

Your liability is limited to $100 unless you declare a higher value. See the FedEx Service Guide for details.

Credit Card Auth.

8 Release Signature — Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

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