

# AndroGel®

(testosterone gel) 1%



R<sub>x</sub> only

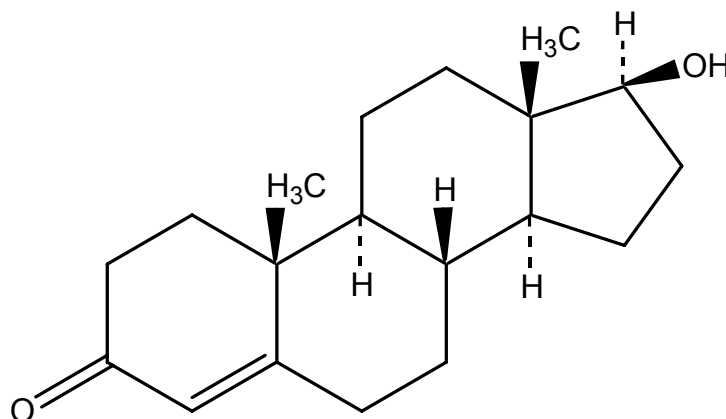
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## 4 DESCRIPTION

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

9 A daily application of AndroGel® 5 g, 7.5 g, or 10 g contains 50 mg, 75 mg, or 100  
10 mg of testosterone, respectively, to be applied daily to the skin's surface.  
11 Approximately 10% of the applied testosterone dose is absorbed across skin of average  
12 permeability during a 24-hour period.

13 The active pharmacologic ingredient in AndroGel® is testosterone. Testosterone  
14 USP is a white to practically white crystalline powder chemically described as 17-beta  
15 hydroxyandrost-4-en-3-one.  
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19 **Testosterone**

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21  $C_{19}H_{28}O_2$

MW 288.42

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23 Inactive ingredients in AndroGel® are ethanol 67.0%, purified water, sodium hydroxide,  
24 carbomer 940 and isopropyl myristate; these ingredients are not pharmacologically  
25 active.  
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## 27 CLINICAL PHARMACOLOGY

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

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32 **Testosterone - General Androgen Effects:**  
33 Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are  
34 responsible for the normal growth and development of the male sex organs and for  
35 maintenance of secondary sex characteristics. These effects include the growth and  
36 maturation of prostate, seminal vesicles, penis, and scrotum; the development of male  
37 hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement,  
38 vocal chord thickening, alterations in body musculature, and fat distribution.  
39 Testosterone and DHT are necessary for the normal development of secondary sex  
40 characteristics. Male hypogonadism results from insufficient secretion of testosterone  
41 and is characterized by low serum testosterone concentrations. Symptoms associated  
42 with male hypogonadism include impotence and decreased sexual desire, fatigue and  
43 loss of energy, mood depression, regression of secondary sexual characteristics and  
44 osteoporosis. Hypogonadism is a risk factor for osteoporosis in men.

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

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

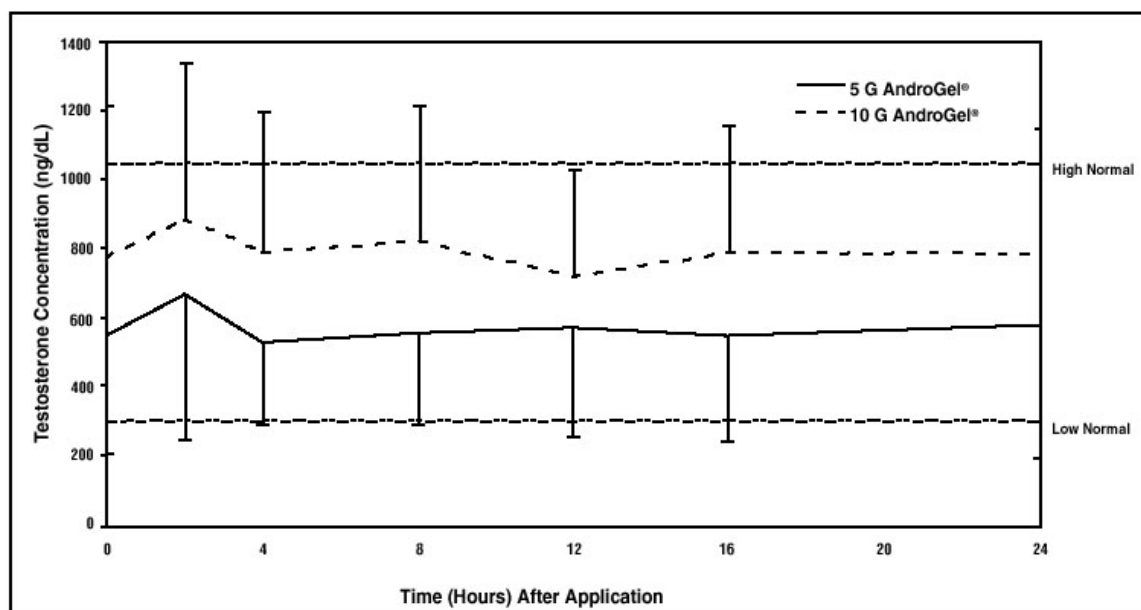
56 During exogenous administration of androgens, endogenous testosterone release  
57 may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At  
58 large doses of exogenous androgens, spermatogenesis may also be suppressed  
59 through feedback inhibition of pituitary follicle-stimulating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

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

## 62 63 **Pharmacokinetics**

64 **Absorption:** AndroGel® is a hydroalcoholic formulation that dries quickly when applied  
65 to the skin surface. The skin serves as a reservoir for the sustained release of  
66 testosterone into the systemic circulation. Approximately 10% of the testosterone dose  
67 applied on the skin surface from AndroGel® is absorbed into systemic circulation.  
68 Therefore, 5 g and 10 g of AndroGel® systemically delivers approximately 5 mg and 10  
69 mg of testosterone, respectively. In a study with 10 g of AndroGel®, all patients showed  
70 an increase in serum testosterone within 30 minutes, and eight of nine patients had a  
71 serum testosterone concentration within normal range by 4 hours after the initial  
72 application. Absorption of testosterone into the blood continues for the entire 24-hour  
73 dosing interval. Serum concentrations approximate the steady-state level by the end of  
74 the first 24 hours and are at steady state by the second or third day of dosing.

75 With single daily applications of AndroGel®, follow-up measurements 30, 90 and  
76 180 days after starting treatment have confirmed that serum testosterone  
77 concentrations are generally maintained within the eugonadal range. Figure 1  
78 summarizes the 24-hour pharmacokinetic profiles of testosterone for patients  
79 maintained on 5 g or 10 g of AndroGel® for 30 days. The average ( $\pm$  SD) daily  
80 testosterone concentration produced by AndroGel® 10 g on Day 30 was 792 ( $\pm$  294)  
81 ng/dL and by AndroGel® 5 g 566 ( $\pm$  262) ng/dL.  
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84  
85 **FIGURE 1: Mean ( $\pm$  SD) Steady-State Serum Testosterone Concentrations on Day**  
86 **30 in Patients Applying AndroGel® Once Daily**  
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88 When AndroGel® treatment is discontinued after achieving steady state, serum  
89 testosterone levels remain in the normal range for 24 to 48 hours but return to their  
90 pretreatment levels by the fifth day after the last application.

91 **Distribution:** Circulating testosterone is chiefly bound in the serum to sex hormone-  
92 binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone  
93 easily dissociates from albumin and is presumed to be bioactive. The portion of  
94 testosterone bound to SHBG is not considered biologically active. The amount of SHBG  
95 in the serum and the total testosterone level will determine the distribution of bioactive  
96 and nonbioactive androgen. SHBG-binding capacity is high in prepubertal children,  
97 declines during puberty and adulthood, and increases again during the later decades of  
98 life. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains  
99 unbound (free) and the rest is bound to albumin and other proteins.

100 **Metabolism:** There is considerable variation in the half-life of testosterone as reported  
101 in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various  
102 17-keto steroids through two different pathways. The major active metabolites of  
103 testosterone are estradiol and DHT. DHT binds with greater affinity to SHBG than does

104 testosterone. In many tissues, the activity of testosterone depends on its reduction to  
105 DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is  
106 transported to the nucleus where it initiates transcription and cellular changes related to  
107 androgen action. In reproductive tissues, DHT is further metabolized to 3- $\alpha$  and 3- $\beta$   
108 androstenediol.

109 DHT concentrations increased in parallel with testosterone concentrations during  
110 AndroGel® treatment. After 180 days of treatment, mean DHT concentrations were  
111 within the normal range with 5 g AndroGel® and were about 7% above the normal  
112 range after a 10 g dose. The mean steady-state DHT/T ratio during 180 days of  
113 AndroGel® treatment remained within normal limits (as determined by the analytical  
114 laboratory involved with this clinical trial) and ranged from 0.23 to 0.29 (5 g/day) and  
115 from 0.27 to 0.33 (10 g/day).

116 **Excretion:** About 90% of a dose of testosterone given intramuscularly is excreted in  
117 the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites;  
118 about 6% of a dose is excreted in the feces, mostly in the unconjugated form.  
119 Inactivation of testosterone occurs primarily in the liver.

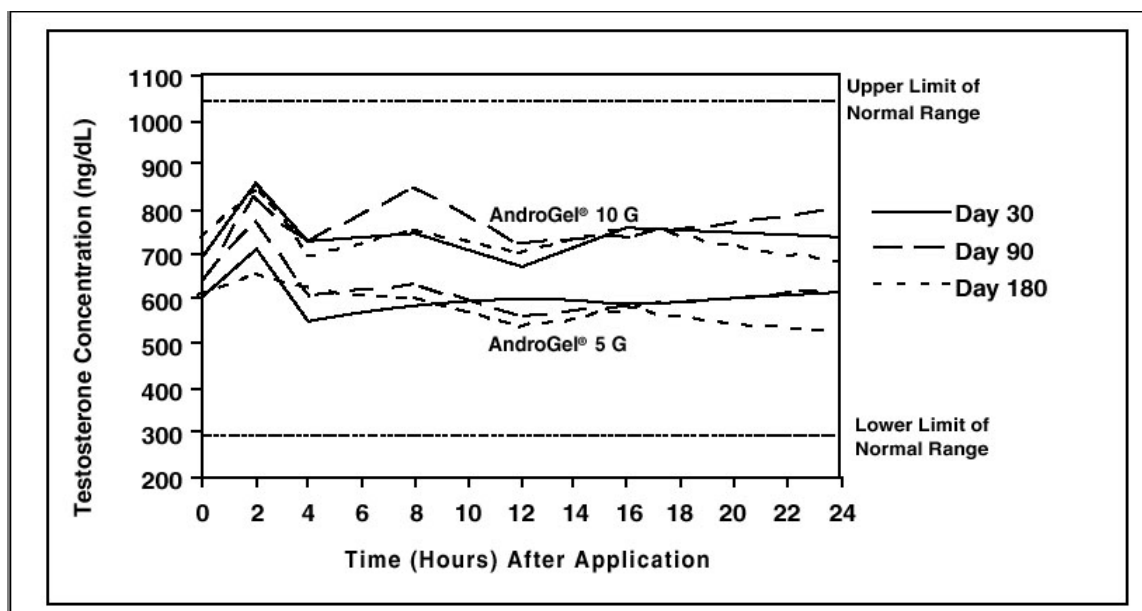
120 **Special Populations:** In patients treated with AndroGel®, there are no observed  
121 differences in the average daily serum testosterone concentration at steady state based  
122 on age, cause of hypogonadism or body mass index. No formal studies were  
123 conducted involving patients with renal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

#### 124 125 Clinical Studies

126 AndroGel® 1% was evaluated in a multicenter, randomized, parallel-group, active-  
127 controlled, 180-day trial in 227 hypogonadal men. The study was conducted in 2  
128 phases. During the Initial Treatment Period (Days 1-90), 73 patients were randomized  
129 to AndroGel® 5 g daily, 78 patients to AndroGel® 10 g daily, and 76 patients to a non-  
130 scrotal testosterone transdermal system. The study was double-blind for dose of  
131 AndroGel® but open-label for active control. Patients who were originally randomized  
132 to AndroGel® and who had single-sample serum testosterone levels above or below the  
133 normal range on Day 60 were titrated to 7.5 g daily on Day 91. During the Extended  
134 Treatment Period (Days 91-180), 51 patients continued on AndroGel® 5 g daily, 52  
135 patients continued on AndroGel® 10 g daily, 41 patients continued on a non-scrotal  
136 testosterone transdermal system (5 mg daily), and 40 patients received AndroGel® 7.5  
137 g daily.

138 Mean peak, trough and average serum testosterone concentrations within the  
139 normal range (298-1043 ng/dL) were achieved on the first day of treatment with doses  
140 of 5 g and 10 g. In patients continuing on AndroGel® 5 g and 10 g, these mean  
141 testosterone levels were maintained within the normal range for the 180-day duration of  
142 the study. Figure 2 summarizes the 24-hour pharmacokinetic profiles of testosterone  
143 administered as AndroGel® for 30, 90 and 180 days. Testosterone concentrations were  
144 maintained as long as the patient continued to properly apply the prescribed AndroGel®  
145 treatment.

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**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)**

	<b>5 g</b> N = 44	<b>7.5 g</b> N = 37	<b>10 g</b> 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. 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®

171 treatment, as did the subjective score for "satisfactory duration of erection." AndroGel®  
172 treatment at 5 g/day and 10 g/day produced positive effects on mood and fatigue.  
173 Similar changes were seen after 180 days of treatment and in the group treated with the  
174 7.5 g dose. DHT concentrations increased in parallel with testosterone concentrations at  
175 AndroGel® doses of 5 g/day and 10 g/day, but the DHT/T ratio stayed within the normal  
176 range, indicating enhanced availability of the major physiologically active androgen.  
177 Serum estradiol (E2) concentrations increased significantly within 30 days of starting  
178 treatment with AndroGel® 5 or 10 g/day and remained elevated throughout the  
179 treatment period but remained within the normal range for eugonadal men. Serum  
180 levels of SHBG decreased very slightly (1 to 11%) during AndroGel® treatment. In men  
181 with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and  
182 time-dependent manner during treatment with AndroGel®.

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

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

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205 **INDICATIONS AND USAGE**

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

- 208 1. Primary hypogonadism (congenital or acquired) - testicular failure due to  
209 cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy,  
210 Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy  
211 metals. These men usually have low serum testosterone levels and gonadotropins  
212 (FSH, LH) above the normal range.  
213 2. Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin  
214 or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-

215 hypothalamic injury from tumors, trauma, or radiation. These men have low  
216 testosterone serum levels but have gonadotropins in the normal or low range.  
217 AndroGel® has not been clinically evaluated in males under 18 years of age.  
218

## 219 **CONTRAINDICATIONS**

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

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

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

230 AndroGel® should not be used in patients with known hypersensitivity to any of its  
231 ingredients, including testosterone USP that is chemically synthesized from soy.  
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## 233 **WARNINGS**

- 234 1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g.,  
235 methyltestosterone) has been associated with serious hepatic adverse effects  
236 (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis  
237 hepatis can be a life-threatening or fatal complication. Long-term therapy with  
238 testosterone enanthate, which elevates blood levels for prolonged periods, has  
239 produced multiple hepatic adenomas. Testosterone is not known to produce these  
240 adverse effects.
- 241 2. Geriatric patients treated with androgens may be at an increased risk for the  
242 development of prostatic hyperplasia and prostatic carcinoma.
- 243 3. Geriatric patients and other patients with clinical or demographic characteristics that  
244 are recognized to be associated with an increased risk of prostate cancer should be  
245 evaluated for the presence of prostate cancer prior to initiation of testosterone  
246 replacement therapy. In men receiving testosterone replacement therapy,  
247 surveillance for prostate cancer should be consistent with current practices for  
248 eugonadal men (see **PRECAUTIONS: Carcinogenesis, Mutagenesis,**  
249 **Impairment of Fertility and Laboratory Tests**).
- 250 4. Edema with or without congestive heart failure may be a serious complication in  
251 patients with preexisting cardiac, renal, or hepatic disease. In addition to  
252 discontinuation of the drug, diuretic therapy may be required.
- 253 5. Gynecomastia frequently develops and occasionally persists in patients being  
254 treated for hypogonadism.
- 255 6. The treatment of hypogonadal men with testosterone esters may potentiate sleep  
256 apnea in some patients, especially those with risk factors such as obesity or chronic  
257 lung diseases.
- 258 7. ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING  
259 UNTIL THE GEL HAS DRIED.

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## 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 88 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**).



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### **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: 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.

348 **ADVERSE REACTIONS**

349 In a controlled clinical study, 154 patients were treated with AndroGel® for up to 6  
350 months (see **Clinical Studies**). Adverse Events possibly, probably or definitely related  
351 to the use of AndroGel® and reported by ≥1% of the patients are listed in Table 2.  
352

353 **TABLE 2: Adverse Events Possibly, Probably or Definitely Related**  
354 **to Use of AndroGel® in the Controlled Clinical Trial**  
355

Adverse Event	Dose of AndroGel®		
	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%

356 \* *Lab test abnormal* occurred in nine patients with one or more of the  
357 following events: elevated hemoglobin or hematocrit, hyperlipidemia,  
358 elevated triglycerides, hypokalemia, decreased HDL, elevated glucose,  
359 elevated creatinine, or elevated total bilirubin.

360 \*\* *Prostate disorders* included five patients with enlarged prostate, one  
361 patient with BPH, and one patient with elevated PSA results.  
362

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

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

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

375 In an uncontrolled pharmacokinetic study of 10 patients, two had adverse events  
376 associated with AndroGel®; these were asthenia and depression in one patient and  
377 increased libido and hyperkinesia in the other. Among 17 patients in foreign clinical  
378 studies there was 1 instance each of acne, erythema and benign prostate adenoma  
379 associated with a 2.5% testosterone gel formulation applied dermally.

380 One hundred six (106) patients have received AndroGel® for up to 1 year in a long-  
381 term follow-up study for patients who completed the controlled clinical trial. The  
382 preliminary safety results from this study are consistent with those reported for the  
383 controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or  
384 definitely related to the use of AndroGel® and reported by at least 1% of the total  
385 number of patients during long-term exposure to AndroGel®.

387 **TABLE 3: Incidence of Adverse Events Possibly, Probably or Definitely**  
388 **Related to the Use of AndroGel® in the Long-Term, Follow-up Study**  
389

Adverse Event	Dose of AndroGel®		
	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%

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

393 \*\* *Prostate disorders* included enlarged prostate, elevated PSA results, and in  
394 one patient, a new diagnosis of prostate cancer; three patients (one taking  
395 7.5 g daily and two taking 10 g daily) discontinued AndroGel® treatment  
396 during the long-term study because of such disorders.  
397

### 398 **DRUG ABUSE AND DEPENDENCE**

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

401 Oral ingestion of AndroGel® will not result in clinically significant serum testosterone  
402 concentrations due to extensive first-pass metabolism.  
403

### 404 **OVERDOSAGE**

405 There is one report of acute overdose by injection of testosterone enanthate:  
406 testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.  
407

### 408 **DOSAGE AND ADMINISTRATION**

409 The recommended starting dose of AndroGel® 1% is 5 g delivering 5 mg of  
410 testosterone systemically, applied once daily (preferably in the morning) to clean, dry,  
411 intact skin of the shoulders and upper arms and/or abdomen. Serum testosterone

412 levels should be measured approximately 14 days after initiation of therapy to ensure  
413 proper dosing. If the serum testosterone concentration is below the normal range, or if  
414 the desired clinical response is not achieved, the daily AndroGel® 1% dose may be  
415 increased from 5 g to 7.5 g and from 7.5 g to 10 g as instructed by the physician.

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

419 AndroGel® must not be applied to the genitals.

420 If using the multi-dose AndroGel® pump, patients should be instructed to prime the  
421 pump before using it for the first time by fully depressing the pump mechanism  
422 (actuation) 3 times and discard this portion of the product to assure precise dose  
423 delivery. After the priming procedure, patients should completely depress the pump one  
424 time (actuation) for every 1.25 g of product required to achieve the daily prescribed  
425 dosage. The product may be delivered directly into the palm of the hand and then  
426 applied to the desired application sites, either one pump actuation at a time or upon  
427 completion of all pump actuations required for the daily dose. Please refer to the chart  
428 below for specific dosing guidelines when the AndroGel® pump is used.  
429

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

430  
431 If using the packets, the entire contents should be squeezed into the palm of the  
432 hand and immediately applied to the application sites. Alternately, patients may  
433 squeeze a portion of the gel from the packet into the palm of the hand and apply to  
434 application sites. Repeat until entire contents have been applied.

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

437  
438 **HOW SUPPLIED**

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

441  
442 AndroGel® 1% is supplied in non-aerosol, metered-dose pumps. The pump is  
443 composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased  
444 in rigid plastic with a polypropylene cap. Each individual packaged 88 g AndroGel®  
445 pump is capable of dispensing 75 g or 60 metered 1.25 g doses.

446  
447 AndroGel® is also supplied in unit-dose aluminum foil packets in cartons of 30. Each  
448 packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

449

<u>NDC Number</u>	<u>Package Size</u>
451 0051-8488-33	88 g pump
452 0051-8425-30	30 packets: 2.5 g per packet

453 0051-8450-30 30 packets: 5 g per packet

454

455 **Keep AndroGel® out of the reach of children.**

456

457 **Storage**

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

460

461 **Disposal**

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

467

468 **Manufactured by:**

469 Laboratoires Besins International  
470 Montrouge, France

471

472 For:

473 Unimed Pharmaceuticals, Inc.  
474 A Solvay Pharmaceuticals, Inc. Company  
475 Marietta, GA 30062-2224, USA

476

477 500122/500127

478 3E Rev 4/2004

479 U.S. Patent No. 6,503,894

480

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482



500100/500121  
4E Rev 4/2004

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2  
3  
4  
5  
6



## Patient Information and Instructions for Using

# AndroGel®

(testosterone gel) **1%**



7

8 Read this information carefully before using AndroGel® [AN drow jel]. The following  
9 information about AndroGel® should not take the place of your doctor's orders or  
10 recommendations. Your doctor will tell you exactly what dose to take, how to safely  
11 take it, and when to take it. Make sure you understand the benefits and risks of  
12 AndroGel® before you use it. If you have any other questions about your AndroGel®  
13 therapy, ask your doctor or pharmacist.

14

### 15 **What is AndroGel®?**

16 AndroGel® is a clear, colorless gel medicine that delivers testosterone into your body  
17 through your skin. Once AndroGel® is absorbed through your skin, it enters your  
18 bloodstream and helps your body reach normal testosterone levels. The type of  
19 testosterone delivered by AndroGel® is the same as the testosterone produced in your  
20 body.

21

22 Your doctor has prescribed this therapy because your body is not making enough  
23 testosterone. The medical term for this condition is hypogonadism. Testosterone helps  
24 the body produce sperm and the male sexual characteristics. Testosterone is also  
25 necessary for normal sexual function and sex drive.

26

### 27 **Who should not take AndroGel®?**

28 AndroGel® **must not be used by women** or by those individuals with known  
29 hypersensitivity to any of its components, including individuals who are hypersensitive  
30 to testosterone that is chemically synthesized from soy. Pregnant women should avoid  
31 skin contact with AndroGel® application sites in men. The active ingredient in  
32 AndroGel® is testosterone. (See "Inactive Ingredients" at the end of this leaflet for a list  
33 of the other ingredients.) Testosterone may cause fetal harm.

34

35 You should not use AndroGel® if you have any of the following conditions:

- 36 • prostate cancer (if your doctor knows for sure or suspects it)
- 37 • breast cancer (a rare condition for men)

38

### 39 **How should I use the AndroGel® Pump?**

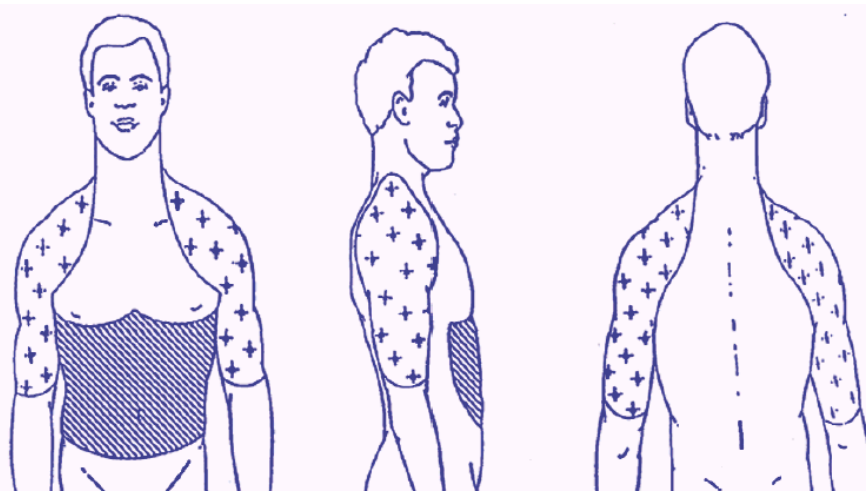
40 It is important that you read and follow these directions on how to use the AndroGel®  
41 pump properly.

- 42 1. **Apply AndroGel® at the same time each day (preferably every morning).** You  
43 should apply your daily dose of gel every morning to clean, dry, intact skin. If you  
44 take a bath or shower in the morning, use AndroGel® **after** your bath or shower.  
45 Your doctor will tell you how much AndroGel® to use each day.
- 46 2. **Be sure your skin is completely dry.**
- 47 3. Before using the pump for the first time, you must prime the AndroGel® pump by  
48 fully depressing the pump three times and discarding the gel. The unused gel  
49 should be discarded by thoroughly rinsing down the sink or discarding in the  
50 household trash in a manner to avoid accidental exposure or ingestion by household  
51 members or pets.
- 52 4. Each full pump depression of either size pump delivers 1.25 g of AndroGel®.  
53 Please refer to the chart below to determine the number of full pump depressions  
54 required for the daily dose prescribed by your doctor:  
55

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

- 56
- 57 5. Fully depress the pump the appropriate number of times to deliver the daily dose  
58 prescribed by your doctor. The product may be delivered directly into the palm of  
59 your hand and then applied to the desired application sites, either one pump  
60 depression at a time or upon completion of all pump depressions required for the  
61 daily dose.  
62

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



- 64 6. **Apply AndroGel® only to healthy, normal skin on your abdomen (stomach**  
65 **area), shoulders, or upper arms.** In this way your body will absorb the right

- 66 amount of testosterone. **Never apply AndroGel® to your genitals (penis or**  
67 **scrotum) or to skin with open sores, wounds, or irritation.**
- 68 7. **Wash your hands with soap and water right away after application to reduce**  
69 **the chance that the medicine will spread from your hands to other people.**
- 70 8. **Let AndroGel® dry for a few minutes before you dress.** This prevents your  
71 clothing from wiping the gel off your skin. It ensures that your body will absorb the  
72 correct amount of testosterone.
- 73 9. **Allow gel to dry completely before smoking or going near an open flame.**
- 74 10. **Wait 5 to 6 hours before showering or swimming.** To ensure that the greatest  
75 amount of AndroGel® is absorbed into your system, you should wait 5 to 6 hours  
76 after application before showering or swimming. Once in a while, you may shower  
77 or swim as soon as 1 hour after applying AndroGel®. If done infrequently, this will  
78 have little effect on the amount of AndroGel® that is absorbed by your body.
- 79 11. **Maintain normal activities.** Once your hands are washed and the application site  
80 is covered with clothing, there is little risk of transferring testosterone to someone  
81 else's skin due to bodily contact. If, however, you expect direct skin contact with  
82 someone else, you should wash your application site(s) with soap and water before  
83 that encounter. This will reduce the chance that the medicine will transfer to the  
84 other person.
- 85 12. The AndroGel® pump contains enough product to allow for priming and a set  
86 number of precise doses. Please refer to the chart below to determine the number  
87 of days of treatment each pump will provide based on your individual dose. Discard  
88 pump afterwards.

89  
90

	<b>Prescribed Daily Dose</b>	<b>Number of Days of Treatment per Pump (after priming)</b>
<b>88 g Pump</b>	5 g	15
	7.5 g	10
	10 g	7.5

91

### 92 **How should I use AndroGel® packets?**

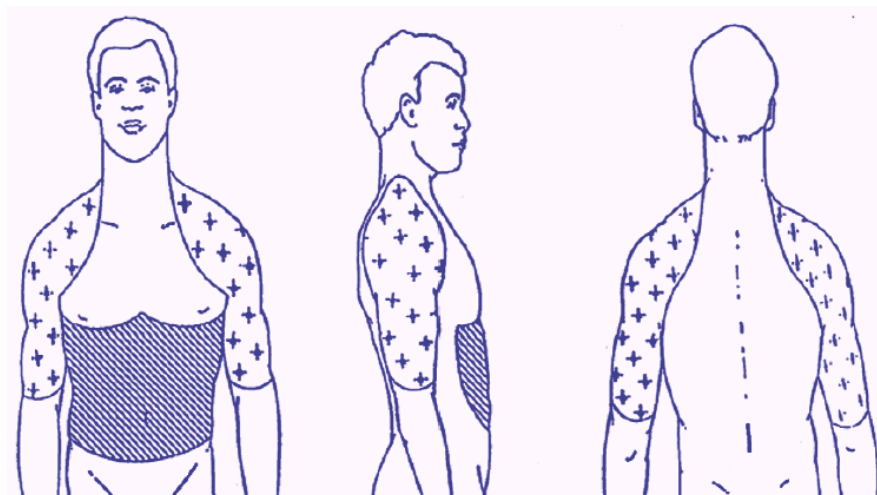
93 It is important that you read and follow these directions on how to use AndroGel®  
94 properly.

- 95 1. **Apply AndroGel® at the same time each day (preferably every morning).** You  
96 should apply your daily dose of gel every morning to clean, dry, intact skin. If you  
97 take a bath or shower in the morning, use AndroGel® **after** your bath or shower.  
98 Your doctor will tell you how much AndroGel® to use each day.
- 99 2. **Be sure your skin is completely dry.**
- 100 3. **Open the packet.** Open one AndroGel® aluminum foil packet by folding the top  
101 edge at the perforation and tearing completely across the packet along the  
102 perforation.



- 103 4. **Remove the contents from the packet. Squeeze the contents into the palm of**  
104 **your hand.** Squeeze from the bottom of the packet toward the top. If you like, you  
105 may squeeze a portion of the gel from the packet into the palm of your hand and  
106 apply to application site(s). **Repeat until the entire contents of the packet have**  
107 **been applied.**

108 Men should apply gel to starred (upper arm/shoulders) or shaded (abdomen) areas only.  
109



- 110  
111 5. **Apply AndroGel® only to healthy, normal skin on your abdomen (stomach**  
112 **area), shoulders, or upper arms.** In this way your body will absorb the right  
113 amount of testosterone. **Never apply AndroGel® to your genitals (penis or**  
114 **scrotum) or to skin with open sores, wounds, or irritation.**
- 115 6. **Wash your hands with soap and water right away after application to reduce**  
116 **the chance that the medicine will spread from your hands to other people.**
- 117 7. **Let AndroGel® dry for a few minutes before you dress.** This prevents your  
118 clothing from wiping the gel off your skin. It ensures that your body will absorb the  
119 correct amount of testosterone.
- 120 8. **Allow gel to dry completely before smoking or going near an open flame.**
- 121 9. **Wait 5 to 6 hours before showering or swimming.** To ensure that the greatest  
122 amount of AndroGel® is absorbed into your system, you should wait 5 to 6 hours  
123 after application before showering or swimming. Once in a while, you may shower or  
124 swim as soon as 1 hour after applying AndroGel®. If done infrequently, this will  
125 have little effect on the amount of AndroGel® that is absorbed by your body.
- 126 10. **Maintain normal activities.** Once your hands are washed and the application site  
127 is covered with clothing, there is little risk of transferring testosterone to someone  
128 else's skin due to bodily contact. If, however, you expect direct skin contact with  
129 someone else, you should wash your application site(s) with soap and water before  
130 that encounter. This will reduce the chance that the medicine will transfer to the  
131 other person.

132

133 **What to do if someone else is exposed to AndroGel®.**

134 If someone else is exposed to AndroGel® either by direct contact with the gel itself or  
135 indirectly because of contact with your treated skin, that person should wash the area of  
136 contact with soap and water as soon as possible. The longer the gel is in contact with  
137 the skin before washing, the greater is the chance that some testosterone will be  
138 absorbed by the other person. This is especially important for women (especially  
139 pregnant women) and children. They have naturally low levels of testosterone and could  
140 be harmed by it.

141

142 **What to do if you get AndroGel® in your eyes.**

143 If you get AndroGel® in your eyes, rinse your eyes right away with warm clean water to  
144 flush out any AndroGel®. Seek medical attention if needed.

145

146 **What to do if you miss a dose.**

147 If you miss a dose, do not double your next dose the next day to catch up. If your next  
148 dose is less than 12 hours away, it is best just to wait. Do not take the skipped dose. If  
149 it is more than 12 hours until your next dose, take the dose you missed. Resume your  
150 normal dosing the next day.

151

152 **What should I avoid while using AndroGel®?**

153 It is important that you do not spread the medicine to others, especially women and  
154 children. Be sure to wash your hands after applying AndroGel®. Do not allow other  
155 persons to contact your skin where you have applied AndroGel®, especially pregnant or  
156 nursing women. **Testosterone may harm the developing baby. ALCOHOL BASED  
157 GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL  
158 HAS DRIED.**

159

160 **What are the possible side effects of AndroGel®?**

161 AndroGel® may cause the following side effects:

- 162 • breast development and breast discomfort
- 163 • extra fluid in the body. This may cause serious problems for patients with heart,  
164 kidney, or liver damage.
- 165 • sleep disturbance called “sleep apnea.” This is more likely in patients who are  
166 overweight or who have lung disease.
- 167 • prostate enlargement, sometimes accompanied by difficulty urinating
- 168 • emotional problems like depression
- 169 • changes in blood levels of cholesterol. This may be monitored and prevented by  
170 periodic blood tests.

171

172 Tell your doctor if you develop any of the following side effects:

- 173 • penis erections that are too frequent or continue too long
- 174 • nausea, vomiting, yellow or darker skin (jaundice), or ankle swelling
- 175 • breathing problems, including problems breathing while sleeping

- 176 • difficulty urinating
- 177 • any side effect that concerns you

178  
179 Tell your doctor about other medicines you are taking. AndroGel® may affect how  
180 these medicines work, and you may need to have your doses adjusted.

181  
182 Tell your doctor if your female partner develops changes in hair distribution, increases in  
183 acne, or other signs of masculinity.

184  
185 Older patients may be at increased risk of developing enlarged prostate or prostate  
186 cancer. This also may be monitored by periodic blood tests and prostate exams.

187  
188 **Disposal**

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

194  
195 **Other Information**

196 Never share your AndroGel® with anyone. Every patient is different. Your doctor has  
197 prescribed AndroGel® specifically for your needs. Use AndroGel® only for the  
198 condition for which it was prescribed. Medicines are sometimes prescribed for  
199 purposes other than those described in a patient information leaflet. If you have any  
200 questions or concerns about your AndroGel® treatment, ask your health care provider  
201 or pharmacist. They can answer your questions and give you the printed information  
202 about AndroGel® that is written for health professionals.

203  
204 **Keep AndroGel® out of the reach of children.**

205  
206 **Inactive Ingredients**

207 Ethanol, purified water, sodium hydroxide, Carbomer 940 and isopropyl myristate.

208  
209 **Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP**  
210 **Controlled Room Temperature].**

211  
212 **Manufactured by:**

213 Laboratoires Besins International  
214 Montrouge, France  
215 For Unimed Pharmaceuticals, Inc.  
216 A Solvay Pharmaceuticals, Inc. Company  
217 Marietta, GA 30062-2224

218  
219

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221 4E Rev 4/2004  
222  
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