

# AndroGel®

(testosterone gel) 1%

III

R<sub>x</sub> only

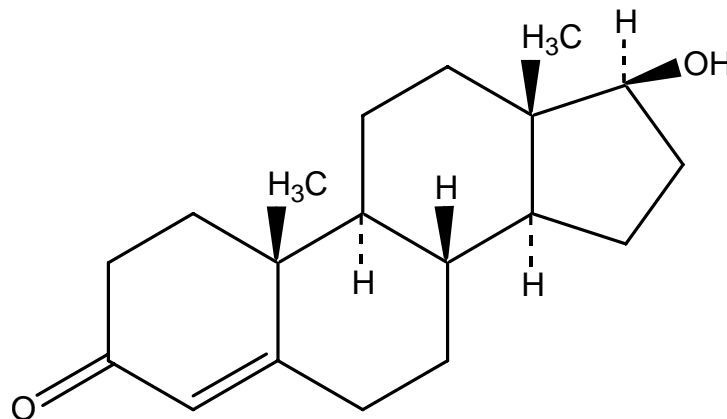
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## DESCRIPTION

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

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

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



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**Testosterone**

C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>

MW 288.42

24 Inactive ingredients in AndroGel® are ethanol 67.0%, purified water, sodium hydroxide,  
25 Carbomer 940 and isopropyl myristate; these ingredients are not pharmacologically  
26 active.

## CLINICAL PHARMACOLOGY

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

### 33 **Testosterone - General Androgen Effects:**

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

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

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

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

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

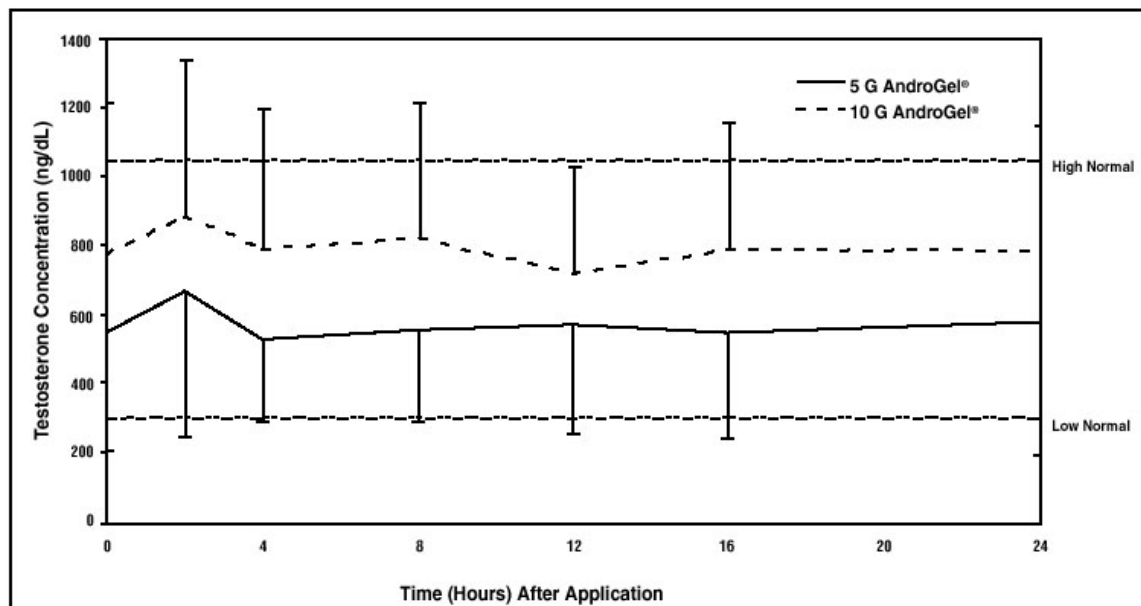
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### 64 **Pharmacokinetics**

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

76 With single daily applications of AndroGel®, follow-up measurements 30, 90 and  
77 180 days after starting treatment have confirmed that serum testosterone  
78 concentrations are generally maintained within the eugonadal range. Figure 1

79 summarizes the 24-hour pharmacokinetic profiles of testosterone for patients  
80 maintained on 5 g or 10 g of AndroGel® for 30 days. The average ( $\pm$  SD) daily  
81 testosterone concentration produced by AndroGel® 10 g on Day 30 was 792 ( $\pm$  294)  
82 ng/dL and by AndroGel® 5 g 566 ( $\pm$  262) ng/dL.  
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85  
86 **FIGURE 1: Mean ( $\pm$  SD) Steady-State Serum Testosterone Concentrations on Day**  
87 **30 in Patients Applying AndroGel® Once Daily**  
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89 When AndroGel® treatment is discontinued after achieving steady state, serum  
90 testosterone levels remain in the normal range for 24 to 48 hours but return to their  
91 pretreatment levels by the fifth day after the last application.

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

101 **Metabolism:** There is considerable variation in the half-life of testosterone as reported  
102 in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various  
103 17-keto steroids through two different pathways. The major active metabolites of  
104 testosterone are estradiol and DHT. DHT binds with greater affinity to SHBG than does  
105 testosterone. In many tissues, the activity of testosterone depends on its reduction to  
106 DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is  
107 transported to the nucleus where it initiates transcription and cellular changes related to

108 androgen action. In reproductive tissues, DHT is further metabolized to 3- $\alpha$  and 3- $\beta$   
109 androstenediol.

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

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

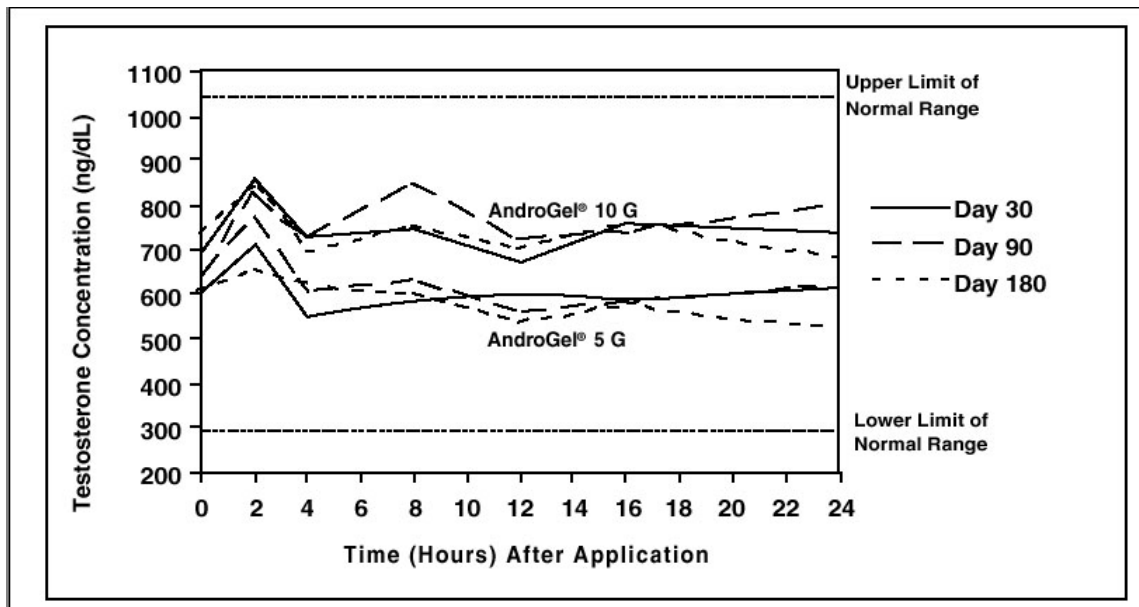
121 **Special Populations:** In patients treated with AndroGel®, there are no observed  
122 differences in the average daily serum testosterone concentration at steady state based  
123 on age, cause of hypogonadism or body mass index. No formal studies were  
124 conducted involving patients with renal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

## 125 126 **CLINICAL STUDIES**

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

139 Mean peak, trough and average serum testosterone concentrations within the  
140 normal range (298-1043 ng/dL) were achieved on the first day of treatment with doses  
141 of 5 g and 10 g. In patients continuing on AndroGel® 5 g and 10 g, these mean  
142 testosterone levels were maintained within the normal range for the 180-day duration of  
143 the study. Figure 2 summarizes the 24-hour pharmacokinetic profiles of testosterone  
144 administered as AndroGel® for 30, 90 and 180 days. Testosterone concentrations were  
145 maintained as long as the patient continued to properly apply the prescribed AndroGel®  
146 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 ( $\pm$  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 $\pm$ 225	601 $\pm$ 309	713 $\pm$ 209
Cmax	830 $\pm$ 347	901 $\pm$ 471	1083 $\pm$ 434
Cmin	371 $\pm$ 165	406 $\pm$ 220	485 $\pm$ 156

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® treatment, as did the subjective score for "satisfactory duration of erection." AndroGel® treatment at 5 g/day and 10 g/day produced positive effects on mood and fatigue.

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

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#### 185 ***Potential for Testosterone Transfer:***

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

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#### 196 **INDICATIONS AND USAGE**

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

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- 200 1. Primary hypogonadism (congenital or acquired) - testicular failure due to  
201 cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy,  
202 Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy  
203 metals. These men usually have low serum testosterone levels and gonadotropins  
204 (FSH, LH) above the normal range.
- 205 2. Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin  
206 or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-  
207 hypothalamic injury from tumors, trauma, or radiation. These men have low  
208 testosterone serum levels but have gonadotropins in the normal or low range.

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

211

#### 212 **CONTRAINDICATIONS**

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

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

217 Pregnant women should avoid skin contact with AndroGel® application sites in men.  
218 Testosterone may cause fetal harm. In the event that unwashed or unclothed skin to  
219 which AndroGel® has been applied does come in direct contact with the skin of a

220 pregnant woman, the general area of contact on the woman should be washed with  
221 soap and water as soon as possible. *In vitro* studies show that residual testosterone is  
222 removed from the skin surface by washing with soap and water.

223 AndroGel® should not be used in patients with known hypersensitivity to any of its  
224 ingredients, including testosterone USP that is chemically synthesized from soy.  
225

## 226 **WARNINGS**

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

## 253 **PRECAUTIONS**

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

- 258 ▪ Patients should wash their hands immediately with soap and water after application  
259 of AndroGel®.
- 260 ▪ Patients should cover the application site(s) with clothing after the gel has dried (e.g.  
261 a shirt).
- 262 ▪ In the event that unwashed or unclothed skin to which AndroGel® has been applied  
263 does come in direct contact with the skin of another person, the general area of  
264 contact on the other person should be washed with soap and water as soon as

265 possible. *In vitro* studies show that residual testosterone is removed from the skin  
266 surface by washing with soap and water.

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

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## 270 **General**

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

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

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## 276 **Information for Patients**

277 Advise patients to carefully read the information brochure that accompanies each carton  
278 of 30 AndroGel® single-use packets, 44 g AndroGel® pump, or 88 g AndroGel® pump.

279 Advise patients of the following:

- 280 ▪ AndroGel® should not be applied to the scrotum.
- 281 ▪ AndroGel® should be applied once daily to clean dry skin.
- 282 ▪ After application of AndroGel®, it is currently unknown for how long showering or  
283 swimming should be delayed. For optimal absorption of testosterone, it appears  
284 reasonable to wait at least 5-6 hours after application prior to showering or  
285 swimming. Nevertheless, showering or swimming after just 1 hour should have a  
286 minimal effect on the amount of AndroGel® absorbed if done very infrequently.
- 287 ▪ Since gels are flammable, avoid fire, flame or smoking during use.

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## 289 **Laboratory Tests**

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

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## 297 **Drug Interactions**

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

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

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

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

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## 309 **Drug/Laboratory Test Interactions**

310 Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total  
311 T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels  
312 remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

313

### 314 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

315 **Animal Data:** Testosterone has been tested by subcutaneous injection and  
316 implantation in mice and rats. In mice, the implant induced cervical-uterine tumors,  
317 which metastasized in some cases. There is suggestive evidence that injection of  
318 testosterone into some strains of female mice increases their susceptibility to hepatoma.  
319 Testosterone is also known to increase the number of tumors and decrease the degree  
320 of differentiation of chemically induced carcinomas of the liver in rats.

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

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

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

330 In men receiving testosterone replacement therapy, surveillance for prostate cancer  
331 should be consistent with current practices for eugonadal men.

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

334 **Nursing Mothers:** AndroGel® is not indicated for women and must not be used in  
335 women.

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

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### 339 **ADVERSE REACTIONS**

340 In a controlled clinical study, 154 patients were treated with AndroGel® for up to 6  
341 months (see **CLINICAL STUDIES**). Adverse Events possibly, probably or definitely  
342 related to the use of AndroGel® and reported by  $\geq 1\%$  of the patients are listed in  
343 Table 2.

344

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

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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%

Adverse Event	Dose of AndroGel®		
	5 g	7.5 g	10 g
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%

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

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

354  
355 The following adverse events possibly related to the use of AndroGel® occurred in  
356 fewer than 1% of patients: amnesia, anxiety, discolored hair, dizziness, dry skin,  
357 hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema,  
358 sweating, and vasodilation.

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

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

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

372 One hundred six (106) patients have received AndroGel® for up to 12 months in a  
373 long-term follow-up study for patients who completed the controlled clinical trial. The  
374 preliminary safety results from this study are consistent with those reported for the  
375 controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or  
376 definitely related to the use of AndroGel® and reported by at least 1% of the total  
377 number of patients during long-term exposure to AndroGel®.

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**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	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%

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\* *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.

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

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

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

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#### **OVERDOSAGE**

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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.

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#### **DOSAGE AND ADMINISTRATION**

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The recommended starting dose of AndroGel® 1% is 5 g delivering 5 mg of testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper dosing. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily AndroGel® 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.

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

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AndroGel® must not be applied to the genitals.

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If using the multi-dose AndroGel® pump, patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. After the priming procedure, patients should completely depress the pump one time (actuation) for every 1.25 g of product required to achieve the daily prescribed

417 dosage. The product may be delivered directly into the palm of the hand and then  
418 applied to the desired application sites, either one pump actuation at a time or upon  
419 completion of all pump actuations required for the daily dose. Please refer to the chart  
420 below for specific dosing guidelines when the AndroGel® pump is used.  
421

Prescribed Daily Dose	Number of Pump Actuations
5 g	4
7.5 g	6
10 g	8

422  
423 If using the packets, the entire contents should be squeezed into the palm of the  
424 hand and immediately applied to the application sites. Alternately, patients may  
425 squeeze a portion of the gel from the packet into the palm of the hand and apply to  
426 application sites. Repeat until entire contents have been applied.

427 Application sites should be allowed to dry for a few minutes prior to dressing. Hands  
428 should be washed with soap and water after AndroGel® has been applied.  
429

### 430 HOW SUPPLIED

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

433  
434 AndroGel® 1% is supplied in non-aerosol, metered-dose pumps. The pump is  
435 composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased  
436 in rigid plastic with a polypropylene cap. Each individual packaged 44 g AndroGel®  
437 pump is capable of dispensing thirty 1.25 g doses; each individual packaged 88 g  
438 AndroGel® pump is capable of dispensing sixty 1.25 g doses.  
439

440 AndroGel® is also supplied in unit-dose aluminum foil packets in cartons of 30. Each  
441 packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.  
442

<u>NDC Number</u>	<u>Strength</u>	<u>Package Size</u>
443 0051-8444-21	1% (440 mg)	44 g pump
444 0051-8488-33	1% (880 mg)	88 g pump
445 0051-8425-30	1% (25 mg)	30 packets: 2.5 g per packet
446 0051-8450-30	1% (50 mg)	30 packets: 5 g per packet

### 448 449 450 Storage

451 Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].  
452

### 453 Disposal

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

459  
460 **Manufactured by:**  
461 Laboratoires Besins International  
462 Montrouge, France  
463  
464 For:  
465 Unimed Pharmaceuticals, Inc.  
466 A Solvay Pharmaceuticals, Inc. Company  
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469 500122/500127  
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471  
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473  
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