

AndroGel®

(testosterone gel) 1%



R_x only

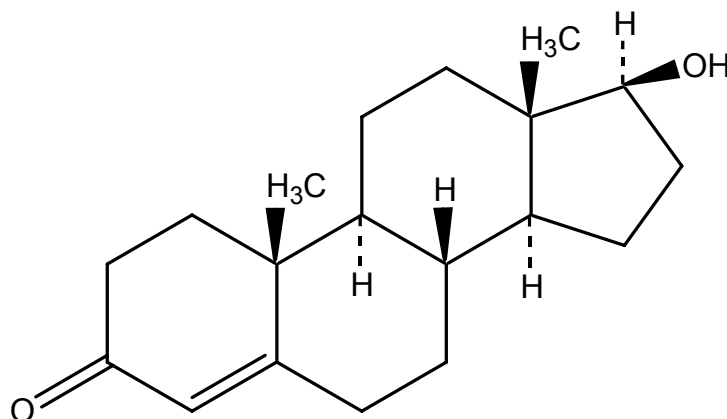
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2 500122/500127
3 3E Rev 4/2004

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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18
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.

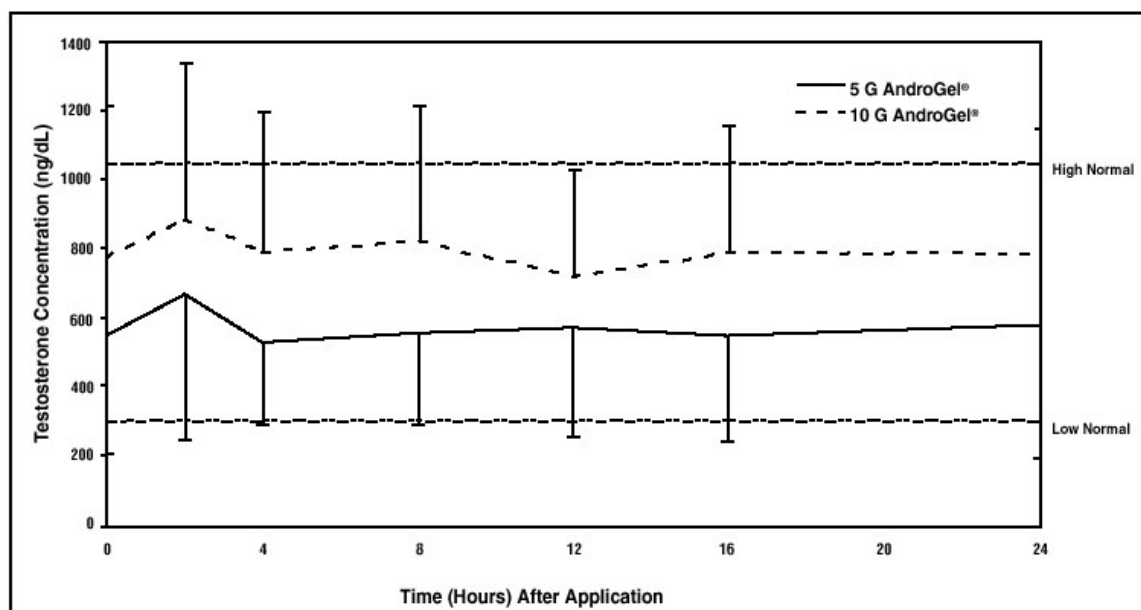
56 During exogenous administration of androgens, endogenous testosterone release
57 may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At
58 large doses of exogenous androgens, spermatogenesis may also be suppressed
59 through feedback inhibition of pituitary follicle-stimulating 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**
87

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- α and 3- β
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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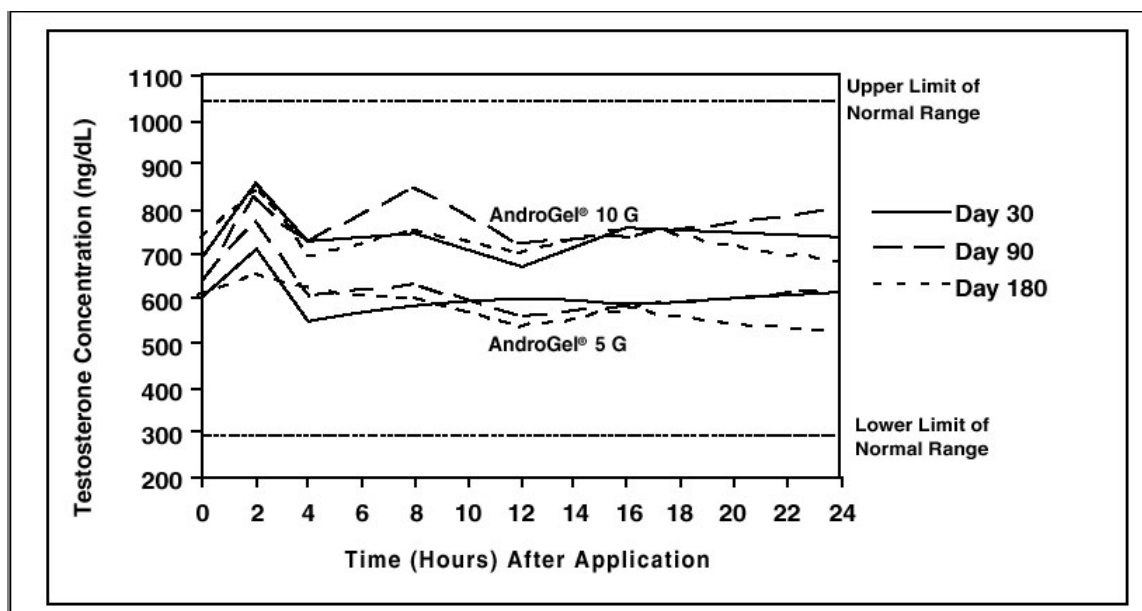


FIGURE 2: Mean Steady-State Testosterone Concentrations in Patients with Once-Daily AndroGel® Therapy

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)

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

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

AndroGel® 5 g/day and 10 g/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment. 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®.

183
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.

193
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.

204 205 **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.
232

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

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481 © 2004 Unimed Pharmaceuticals, Inc.

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500100/500121
4E Rev 4/2004

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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?**

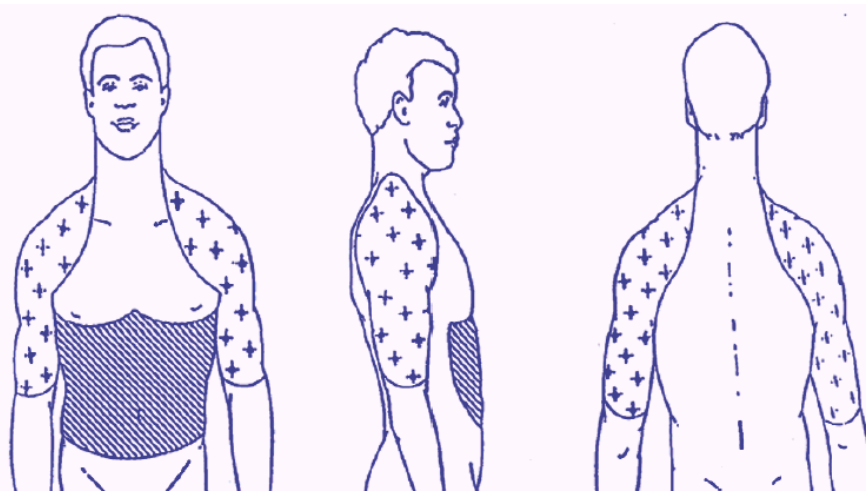
40 It is important that you read and follow these directions on how to use the AndroGel®
41 pump properly.

- 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

| | Prescribed Daily Dose | Number of Days of Treatment per Pump (after priming) |
|------------------|------------------------------|---|
| 88 g Pump | 5 g | 15 |
| | 7.5 g | 10 |
| | 10 g | 7.5 |

91

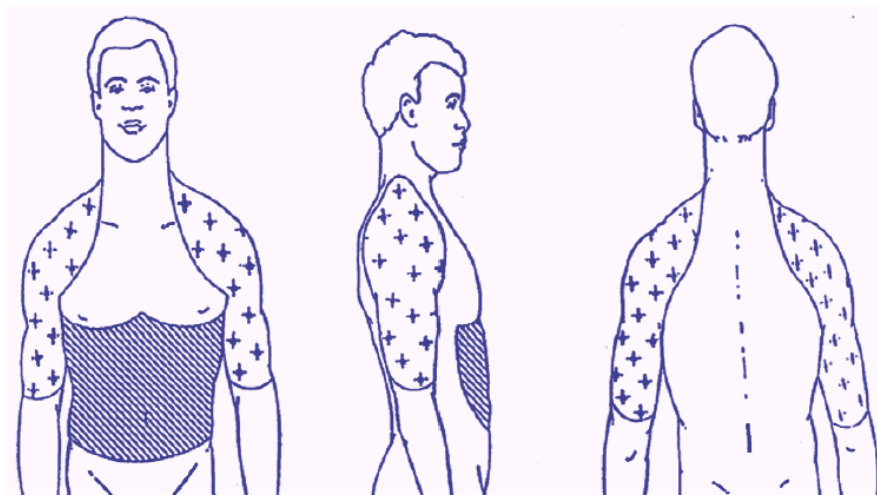
92 **How should I use AndroGel® packets?**

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.

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

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

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

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

What to do if you miss a dose.

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

What should I avoid while using AndroGel®?

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

What are the possible side effects of AndroGel®?

AndroGel® may cause the following side effects:

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

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

- penis erections that are too frequent or continue too long
- nausea, vomiting, yellow or darker skin (jaundice), or ankle swelling
- 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

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220 500100/500121

221 4E Rev 4/2004

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