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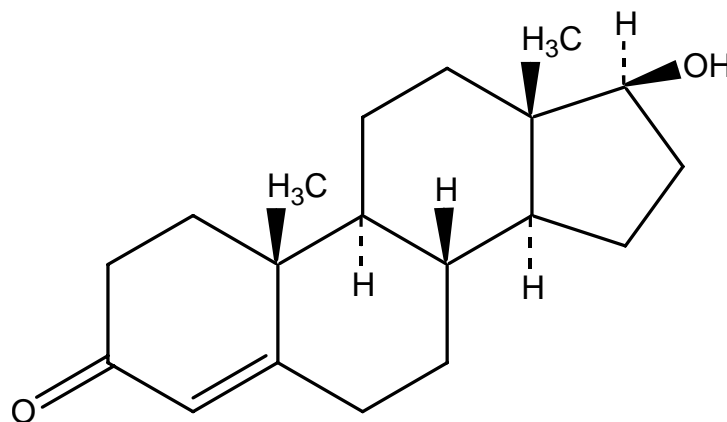
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2 500122/500127 Rev Apr 2007

3 **DESCRIPTION**

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

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

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



16
17
18 **Testosterone**

19
20 $C_{19}H_{28}O_2$

MW 288.42

21
22 Inactive ingredients in AndroGel are ethanol 67.0%, purified water, sodium hydroxide,
23 carbomer 980 and isopropyl myristate; these ingredients are not pharmacologically active.
24

25 **CLINICAL PHARMACOLOGY**

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

29

30 **Testosterone – General Androgen Effects:**

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

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

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

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

54

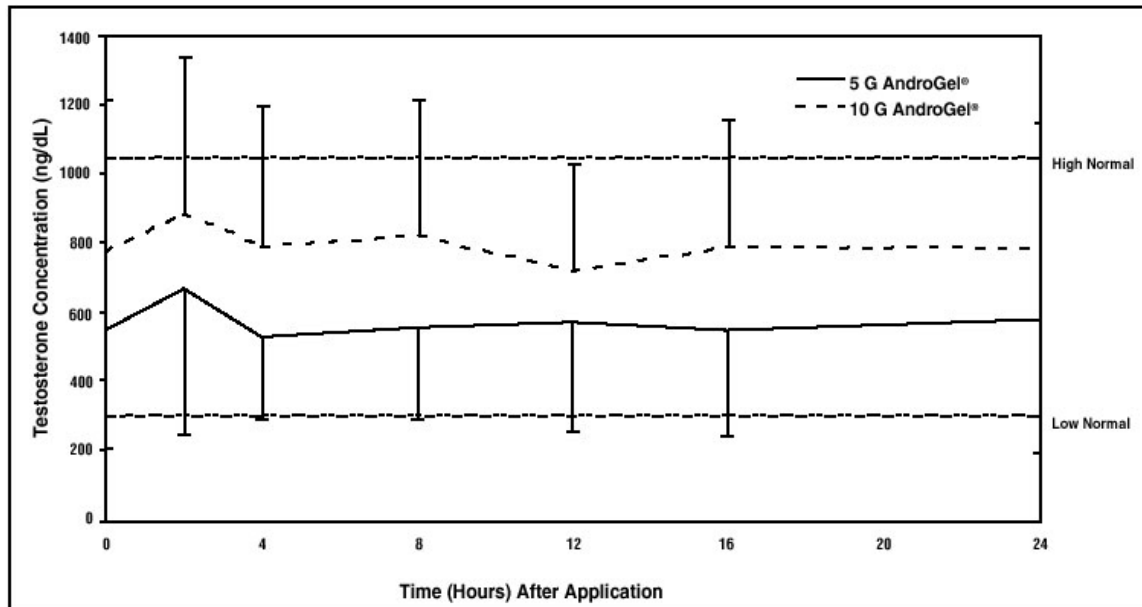
55 **Pharmacokinetics**

56 **Absorption:** AndroGel is a hydroalcoholic formulation that dries quickly when applied to the
57 skin surface. The skin serves as a reservoir for the sustained release of testosterone into the
58 systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface
59 from AndroGel is absorbed into systemic circulation. Therefore, 5 g and 10 g of AndroGel
60 systemically deliver approximately 5 mg and 10 mg of testosterone, respectively. In a study with
61 10 g of AndroGel, all patients showed an increase in serum testosterone within 30 minutes, and
62 eight of nine patients had a serum testosterone concentration within normal range by 4 hours
63 after the initial application. Absorption of testosterone into the blood continues for the entire 24-
64 hour dosing interval. Serum concentrations approximate the steady-state level by the end of the
65 first 24 hours and are at steady state by the second or third day of dosing.

66 With single daily applications of AndroGel, follow-up measurements 30, 90 and 180 days
67 after starting treatment have confirmed that serum testosterone concentrations are generally
68 maintained within the eugonadal range. Figure 1 summarizes the 24-hour pharmacokinetic
69 profiles of testosterone for hypogonadal men (<300 ng/dL) maintained on 5 g or 10 g of
70 AndroGel for 30 days. The average (\pm SD) daily testosterone concentration produced by
71 AndroGel 10 g on Day 30 was 792 (\pm 294) ng/dL and by AndroGel 5 g 566 (\pm 262) ng/dL.

72

73



74 **FIGURE 1: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30 in**
 75 **Patients Applying AndroGel Once Daily**
 76
 77

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

81 **Distribution:** Circulating testosterone is chiefly bound in the serum to sex hormone-binding
 82 globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates
 83 from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not
 84 considered biologically active. The amount of SHBG in the serum and the total testosterone level
 85 will determine the distribution of bioactive and nonbioactive androgen. SHBG-binding capacity
 86 is high in prepubertal children, declines during puberty and adulthood, and increases again
 87 during the later decades of life. Approximately 40% of testosterone in plasma is bound to SHBG,
 88 2% remains unbound (free) and the rest is bound to albumin and other proteins.

89 **Metabolism:** There is considerable variation in the half-life of testosterone as reported in the
 90 literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto
 91 steroids through two different pathways. The major active metabolites of testosterone are
 92 estradiol and DHT. DHT binds with greater affinity to SHBG than does testosterone. In many
 93 tissues, the activity of testosterone depends on its reduction to DHT, which binds to cytosol
 94 receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates
 95 transcription and cellular changes related to androgen action. In reproductive tissues, DHT is
 96 further metabolized to 3- α and 3- β androstanediol.

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

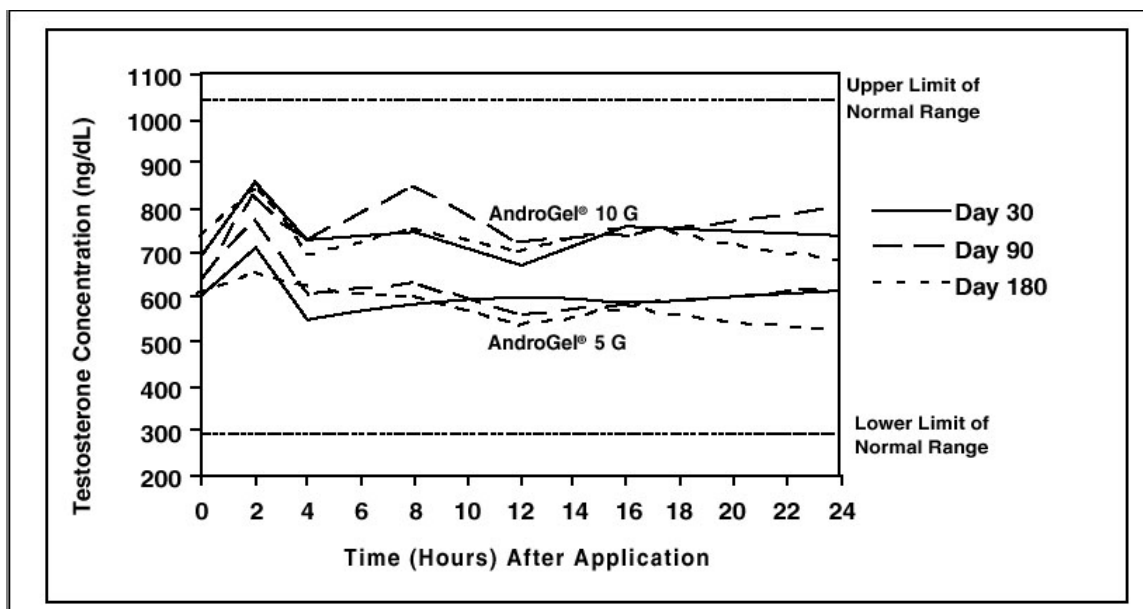
103 **Excretion:** About 90% of a dose of testosterone given intramuscularly is excreted in the urine as
104 glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is
105 excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs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

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

111
112 **Clinical Studies**

113 AndroGel was evaluated in a multicenter, randomized, parallel-group, active-controlled, 180-day
114 trial in 227 hypogonadal men. The study was conducted in 2 phases. During the Initial Treatment
115 Period (Days 1-90), 73 patients were randomized to AndroGel 5 g daily, 78 patients to AndroGel
116 10 g daily, and 76 patients to a non-scrotal testosterone transdermal system. The study was
117 double-blind for dose of AndroGel but open-label for active control. Patients who were
118 originally randomized to AndroGel and who had single-sample serum testosterone levels above
119 or below the normal range on Day 60 were titrated to 7.5 g daily on Day 91. During the
120 Extended Treatment Period (Days 91-180), 51 patients continued on AndroGel 5 g daily, 52
121 patients continued on AndroGel 10 g daily, 41 patients continued on a non-scrotal testosterone
122 transdermal system (5 mg daily), and 40 patients received AndroGel 7.5 g daily. Upon
123 completion of the initial study, 163 enrolled and 162 patients received treatment in an open-label
124 extension study of AndroGel for an additional period of up to 3 years.

125 Mean peak, trough and average serum testosterone concentrations within the normal range
126 (298-1043 ng/dL) were achieved on the first day of treatment with doses of 5 g and 10 g. In
127 patients continuing on AndroGel 5 g and 10 g, these mean testosterone levels were maintained
128 within the normal range for the 180-day duration of the original study. Figure 2 summarizes the
129 24-hour pharmacokinetic profiles of testosterone administered as AndroGel for 30, 90 and 180
130 days. Testosterone concentrations were maintained as long as the patient continued to properly
131 apply the prescribed AndroGel treatment.
132



134 **FIGURE 2: Mean Steady-State Testosterone Concentrations in Patients with**
 135 **Once-Daily AndroGel Therapy**
 136

137 Table 1 summarizes the mean testosterone concentrations on Treatment Day 180 for patients
 138 receiving 5 g, 7.5 g, or 10 g of AndroGel. The 7.5 g dose produced mean concentrations
 139 intermediate to those produced by 5 g and 10 g of AndroGel.
 140

141 **TABLE 1: Mean (\pm SD) Steady-State Serum Testosterone**
 142 **Concentrations During Therapy (Day 180)**
 143

	5 g N = 44	7.5 g N = 37	10 g N = 48
C _{avg}	555 \pm 225	601 \pm 309	713 \pm 209
C _{max}	830 \pm 347	901 \pm 471	1083 \pm 434
C _{min}	371 \pm 165	406 \pm 220	485 \pm 156

144 Of 129 hypogonadal men who were appropriately titrated with AndroGel and who had
 145 sufficient data for analysis, 87% achieved an average serum testosterone level within the normal
 146 range on Treatment Day 180.
 147

148 AndroGel 5 g/day and 10 g/day resulted in significant increases over time in total body mass
 149 and total body lean mass, while total body fat mass and the percent body fat decreased
 150 significantly. These changes were maintained for 180 days of treatment during the original study.
 151 Changes in the 7.5 g dose group were similar. Bone mineral density in both hip and spine
 152 increased significantly from Baseline to Day 180 with 10 g AndroGel.

153 AndroGel treatment at 5 g/day and 10 g/day for 90 days produced significant improvement in
 154 libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as
 155 assessed by patient responses to a questionnaire). The degree of penile erection as subjectively
 156 estimated by the patients, increased with AndroGel treatment, as did the subjective score for
 157 “satisfactory duration of erection.” AndroGel treatment at 5 g/day and 10 g/day produced
 158 positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and
 159 in the group treated with the 7.5 g dose. DHT concentrations increased in parallel with
 160 testosterone concentrations at AndroGel doses of 5 g/day and 10 g/day, but the DHT/T ratio
 161 stayed within the normal range, indicating enhanced availability of the major physiologically
 162 active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of
 163 starting treatment with AndroGel 5 or 10 g/day and remained elevated throughout the treatment
 164 period but remained within the normal range for eugonadal men. Serum levels of SHBG
 165 decreased very slightly (1 to 11%) during AndroGel treatment. In men with hypergonadotropic
 166 hypogonadism, serum levels of LH and FSH fell in a dose- and time-dependent manner during
 167 treatment with AndroGel.
 168

169 **Potential for Phototoxicity:** The phototoxic potential of AndroGel was evaluated in a double-
 170 blind, single-dose study in 27 subjects with photosensitive skin types. The Minimal Erythema
 171 Dose (MED) of ultraviolet radiation was determined for each subject. A single 24 (+1) hour
 172 application of duplicate patches containing test articles (placebo gel, testosterone gel, or saline)
 173 was made to naive skin sites on Day 1. On Day 2, each subject received five exposure times of
 174 ultraviolet radiation, each exposure being 25% greater than the previous one. Skin evaluations

175 were made on Days 2-5. Exposure of test and control article application sites to ultraviolet light
176 did not produce increased inflammation relative to non-irradiated sites, indicating no phototoxic
177 effect.

178
179 **Potential for Testosterone Transfer:** The potential for dermal testosterone transfer following
180 AndroGel use was evaluated in a clinical study between males dosed with AndroGel and their
181 untreated female partners. Two to 12 hours after AndroGel (10 g) application by the male
182 subjects, the couples (N=38 couples) engaged in daily, 15-minute sessions of vigorous skin-to-
183 skin contact so that the female partners gained maximum exposure to the AndroGel application
184 sites. Under these study conditions, all unprotected female partners had a serum testosterone
185 concentration > 2 times the baseline value at some time during the study. When a shirt covered
186 the application site(s), the transfer of testosterone from the males to the female partners was
187 completely prevented.

188

189 **INDICATIONS AND USAGE**

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

- 192 1. Primary hypogonadism (congenital or acquired) – testicular failure due to cryptorchidism,
193 bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter’s syndrome,
194 chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low
195 serum testosterone levels and gonadotropins (FSH, LH) above the normal range.
- 196 2. Hypogonadotropic hypogonadism (congenital or acquired) – idiopathic gonadotropin or
197 luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury
198 from tumors, trauma, or radiation. These men have low testosterone serum levels but have
199 gonadotropins in the normal or low range.

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

201

202 **CONTRAINDICATIONS**

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

205 Pregnant women should avoid skin contact with AndroGel application sites in men.

206 Testosterone may cause fetal harm. In the event that unwashed or unclothed skin to which
207 AndroGel has been applied does come in direct contact with the skin of a pregnant woman, the
208 general area of contact on the woman should be washed with soap and water as soon as possible.

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

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

213

214 **WARNINGS**

- 215 1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g.,
216 methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis,
217 hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-
218 threatening or fatal complication. Long-term therapy with testosterone enanthate, which
219 elevates blood levels for prolonged periods, has produced multiple hepatic adenomas.

220 AndroGel is not known to produce these adverse effects.

- 221 2. Geriatric patients treated with androgens may be at an increased risk for the development of
222 prostatic hyperplasia and prostatic carcinoma.
- 223 3. Geriatric patients and other patients with clinical or demographic characteristics that are
224 recognized to be associated with an increased risk of prostate cancer should be evaluated for
225 the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men
226 receiving testosterone replacement therapy, surveillance for prostate cancer should be
227 consistent with current practices for eugonadal men. Increases in serum PSA from baseline
228 values were seen in approximately 18% of individuals in an open label study of 162
229 hypogonadal men treated with AndroGel for up to 42 months. Most of these increases were
230 seen within the first year of therapy. (see **ADVERSE REACTIONS** and **PRECAUTIONS:**
231 **Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests**).
- 232 4. Due to lack of sufficient, controlled clinical evaluations and the potential for virilizing
233 effects, safe use of AndroGel in women has not been established and AndroGel should not be
234 used in women.
- 235 5. Edema with or without congestive heart failure may be a serious complication in patients
236 with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug,
237 diuretic therapy may be required.
- 238 6. Gynecomastia may develop and may persist in patients being treated for hypogonadism.
- 239 7. The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in
240 some patients, especially those with risk factors such as obesity or chronic lung diseases.
- 241 8. Androgens should be used with caution in cancer patients at risk of hypercalcemia (and
242 associated hypercalciuria). Regular monitoring of serum calcium concentrations is
243 recommended in these patients.
- 244 9. ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING
245 UNTIL THE GEL HAS DRIED.

246 247 **PRECAUTIONS**

- 248 1. Transfer of testosterone to others (including women and children) can occur when vigorous
249 skin-to-skin contact is made with the application site (see **Clinical Studies**). The
250 following precautions are recommended to minimize potential transfer of testosterone
251 from AndroGel-treated skin to another person:
- 252 • Patients should wash their hands immediately with soap and water after application of
253 AndroGel.
 - 254 • Patients should cover the application site(s) with clothing after the gel has dried (e.g. a shirt).
 - 255 • In the event that unwashed or unclothed skin to which AndroGel has been applied does come
256 in direct contact with the skin of another person, the general area of contact on the other
257 person should be washed with soap and water as soon as possible. *In vitro* studies show that
258 residual testosterone is removed from the skin surface by washing with soap and water.
 - 259 • Changes in body hair distribution, significant increase in acne, or other signs of virilization of
260 the female partner should be brought to the attention of a physician.
- 261 2. During exogenous administration of androgens, endogenous testosterone release may be
262 inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses
263 of exogenous androgens, spermatogenesis may also be suppressed through feedback
264 inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to
265 azoospermia.
- 266

267 **General**

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

- 269 • Too frequent or persistent erections of the penis.
270 • Any nausea, vomiting, changes in skin color, or ankle swelling.
271 • Breathing disturbances, including those associated with sleep, or excessive daytime
272 sleepiness.
273 • Changes in urinary habits. (eg, increased nocturia, hesitancy, frequency, urgency, urge,
274 incontinence, urinary retention, and weak flow.)
275

276 **Information for Patients**

277 Advise patients to carefully read the information brochure that accompanies each carton of 30
278 AndroGel single-use packets or 75 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 swimming
283 should be delayed. For optimal absorption of testosterone, it appears reasonable to wait at
284 least 5-6 hours after application prior to showering or swimming. Nevertheless, showering or
285 swimming after just 1 hour should have a minimal effect on the amount of AndroGel
286 absorbed if done very infrequently.
287 • Testosterone gel is not known to have an influence on the ability to drive or use machines;
288 however, no studies have been conducted with AndroGel.
289 • SINCE ALCOHOL BASED GELS ARE FLAMMABLE, AVOID FIRE, FLAME OR
290 SMOKING UNTIL THE GEL HAS DRIED.
291

292 **Drug Interactions**

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

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

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

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

303 **Oral anticoagulants:** Changes in anticoagulant activity (the increased effect of the oral
304 anticoagulant by modification of coagulation factor, hepatic synthesis, and competitive inhibition
305 of plasma protein binding): INR determinations and increased monitoring of the prothrombin
306 time are recommended, especially at the initiation and termination of androgen therapy.
307

308 **Drug/Laboratory Test Interactions**

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

313 See **DOSAGE AND ADMINISTRATION** - Monitoring, Table 5: Recommended
314 Monitoring For Men On Testosterone Replacement Therapy for an overview of efficacy and
315 safety monitoring recommended be performed on men using AndroGel.
316

317 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

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

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

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

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

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

342 Geriatric patients and other patients with clinical or demographic characteristics that are
343 recognized to be associated with an increased risk of prostate cancer should be evaluated for the
344 presence of prostate cancer prior to initiation of testosterone replacement therapy.
345

346 **ADVERSE REACTIONS**

347 **In Clinical Studies**

348 In a controlled clinical study, 154 patients were treated with AndroGel for up to 6 months (see
349 **Clinical Studies**). The most frequently observed adverse events were skin disorders. Adverse
350 Events possibly, probably or definitely related to the use of AndroGel and reported by $\geq 1\%$ of
351 the patients are listed in Table 2.
352
353

354 **TABLE 2: Adverse Events Possibly, Probably or Definitely Related**
355 **to Use of AndroGel in the 180-Day Controlled Clinical Trial**
356

Adverse Event	Dose of AndroGel
---------------	------------------

	5 g n = 77	7.5 g n = 40	10 g n = 78
Acne	1%	3%	8%
Alopecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder***	3%	0%	0%

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

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

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

365

366 The following adverse events possibly related to the use of AndroGel occurred in fewer than
367 1% of patients: amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility,
368 impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

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

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

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

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

385

386
387
388
389

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

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

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

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

396 ** *Testis disorder* included three patients. There were two patients with a non-palpable
397 testis and one patient with slight right testicular tenderness.

398

399 Two patients reported serious adverse events considered possibly related to treatment: deep
400 vein thrombosis (DVT) and prostate disorder requiring a transurethral resection of the prostate
401 (TURP). Nine patients discontinued treatment due to adverse events possibly related to
402 treatment with AndroGel, including two patients with application site reactions, one with kidney
403 failure, and five with prostate disorders (including increase in serum PSA in 4 patients, and
404 increase in PSA with prostate enlargement in a fifth patient). All patients who discontinued due
405 to an increase in serum PSA did so by Day 357.

406

407 *Increases in Serum PSA*

408 During the initial 6-month study, the mean change in PSA values had a statistically significant
409 increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter. While there was
410 no statistically significant increase in mean PSA from 6 months through 36 months of AndroGel
411 treatment for the overall group of 162 patients enrolled in the long-term extension study, there
412 were increases in serum PSA seen in approximately 18% of individual patients. In the long-term
413 extension study, the overall mean change from baseline in serum PSA values for the entire group
414 was 0.11 ng/mL.

415 Twenty-nine (29) (18%) patients met the per-protocol criterion for increase in serum PSA
416 value, defined as a value $\geq 2X$ the baseline value or any single absolute value ≥ 6 ng/mL.

417 Twenty-five of these patients met this criterion by virtue of a post-baseline value at least twice
418 the baseline value. In most of these cases (22/25), the maximum serum PSA value attained was

419 ≤ 2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen
420 at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%).

421 Four patients met this criterion by having a serum PSA ≥ 6 ng/mL and in these, maximum
422 serum PSA values were 6.2 ng/mL, 6.6 ng/mL, 6.7 ng/mL, and 10.7 ng/mL (in AndroGel-treated
423 patients). In two of these AndroGel-treated patients, prostate cancer was detected on biopsy.
424 The first patient's PSA levels were 4.7 ng/mL and 6.2 ng/mL at baseline and at Month 6/Final,
425 respectively. The second patient's PSA levels were 4.2 ng/mL, 5.2 ng/mL, 5.8 ng/mL, and 6.6
426 ng/mL at baseline, Month 6, Month 12, and Final, respectively.

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428 **Postmarketing Experience**

429 Table 4 includes adverse reactions spontaneously reported from Postmarketing experience and
430 general effects of testosterone. Because the reactions are reported voluntarily from a population
431 of uncertain size it is not possible to reliably estimate their frequency or establish a causal
432 relationship to drug exposure.

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434 **Table 4: ADVERSE DRUG REACTIONS FROM POSTMARKETING EXPERIENCE**
435 **OF ANDROGEL AND KNOWN REACTIONS OF GENERAL TESTOSTERONE**

436

TREATMENT ORDERED BY MedDRA SOC:

Blood and the lymphatic system disorders:	Elevated Hgb, Hct (polycythemia)
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders and administration site reactions:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination
Hepatobiliary disorders:	Abnormal liver function tests (e.g. transaminases, elevated GCTP, bilirubin)
Investigations:	Elevated PSA, electrolyte changes (nitrogen, calcium, potassium, phosphorus, sodium), changes in serum lipids (hyperlipidemia, elevated triglycerides, decreased HDL), impaired glucose tolerance, fluctuating testosterone levels, weight increase
Neoplasms benign, malignant and unspecified (cysts and polyps):	Prostate cancer
Nervous system:	Headache, dizziness, sleep apnea, insomnia
Psychiatric disorders:	Depression, emotional lability, decreased libido, nervousness, hostility, amnesia, anxiety
Reproductive system and breast disorders:	Gynecomastia, mastodynia, prostatic enlargement, testicular atrophy, oligospermia, priapism (frequent or prolonged erections)
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (pruritus, dry skin, erythema, rash, discolored hair, paresthesia), sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes)

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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.

OVERDOSAGE

No reports of AndroGel overdose have been received. However, there is one report of acute overdose by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident. It would be most unlikely that such plasma testosterone concentrations be achieved using the transdermal route.

DOSAGE AND ADMINISTRATION

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

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

AndroGel must not be applied to the genitals.

If using the multi-dose AndroGel Pump, patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. After the priming procedure, patients should completely depress the pump one time (actuation) for every 1.25 g of product required to achieve the daily prescribed dosage. The product may be delivered directly into the palm of the hand and then applied to the desired application sites, either one pump actuation at a time or upon completion of all pump actuations required for the daily dose. Alternatively, the product can be applied directly to the application sites. Application directly to the sites may prevent loss of product that may occur during transfer from the palm of the hand onto the application sites. Please refer to the chart below for specific dosing guidelines when the AndroGel Pump is used.

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

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

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

478 **Monitoring**

479 **TABLE 5: Recommended Monitoring For Men On Testosterone Replacement Therapy**

Monitoring Parameters	Month			
	Baseline	1	3	12*
Efficacy				
Testosterone	X	X	X	X
BMD [‡]	X			
Hypogonadism Symptoms	Evaluate patients for physical manifestations of efficacy (i.e., symptoms of hypogonadism) at all office visits or as needed based on patient complaints.			
Safety				
PSA [†]	X		X [§]	X
DRE	X		X [§]	X
Hct/Hgb	X		X	X
Lipids	X			X
LFTs	X			X
Edema Gynecomastia LUTS Sleep Apnea	Evaluate patients for physical manifestations of adverse events at all office visits.			

BMD = bone mineral density; PSA = prostate-specific antigen; DRE = digital rectal examination; Hct = hematocrit; Hgb = hemoglobin; LFTs = liver function tests; LUTS = lower urinary tract symptoms.

*All guidelines recommend annual monitoring following the first year of testosterone replacement therapy.

[†] Clinicians must be mindful of interassay and intra-individual (biologic) variation when monitoring PSA over time. Baseline PSA measurement (e.g. interassay variability increases with higher mean PSA concentrations; intra-individual variability increases with lower PSA concentrations) and assay platform used are factors that influence variability. Coefficients of variation can approximate up to 15% for each.

[§]Following the initial 3-month PSA and DRE evaluation, men should be followed in accordance with updated prostate cancer detection guidelines based on age and race.

[‡]Monitor BMD every two years if considered an important clinical parameter for the patient.

480 **HOW SUPPLIED**

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

483 AndroGel is supplied in non-aerosol, metered-dose pumps. The pump is composed of plastic
484 and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a
485 polypropylene cap. Each individual packaged AndroGel Pump is capable of dispensing 75 g or
486 60 metered 1.25 g doses.

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

<u>NDC Number</u>	<u>Package Size</u>
491 0051-8488-88	2 x 75 g pumps (each pump dispenses 60 metered 1.25 g doses)
492 0051-8425-30	30 packets (2.5 g per packet)
493 0051-8450-30	30 packets (5 g per packet)

494 **Keep AndroGel out of the reach of children.**

495 **Storage**

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

498 **Disposal**

499 Used AndroGel pumps or used AndroGel packets should be discarded in household trash in a
500 manner that prevents accidental application or ingestion by children or pets. In addition, any
501
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503 discarded gel should be thoroughly rinsed down the sink or discarded in the household trash in a
504 manner that prevents accidental application or ingestion by children or pets.

505

506 **Manufactured by:**

507 Laboratoires Besins International

508 Montrouge, France

509

510 For:

511 Unimed Pharmaceuticals, Inc.

512 A Solvay Pharmaceuticals, Inc. Company

513 Marietta, GA 30062-2224, USA

514

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