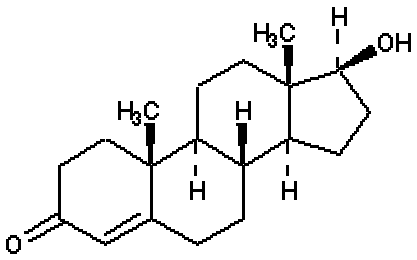
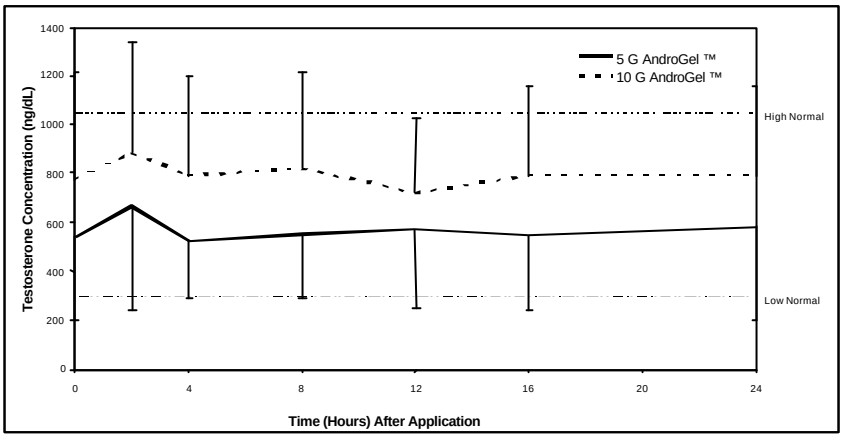
	PROPOSED LABELING TEXT
1.	**AndroGel™ 1%**
2.	**(testosterone gel) C III**
3.	
4.	**DESCRIPTION**
5.	
6.	AndroGel™ (testosterone gel) is a clear, colorless hydroalcoholic gel
7.	containing 1% testosterone. AndroGel™ provides continuous transdermal
8.	delivery of testosterone, the primary circulating endogenous androgen, for 24
9.	hours following a single application to intact, clean, dry skin of the shoulders,
10.	upper arms and/or abdomen.
11.	
12.	A daily application of AndroGel™ 5 G, 7.5 G, or 10 G delivers 50 mg, 75
13.	mg, or 100 mg of testosterone, respectively, per day, to the skin's surface.
14.	Approximately 10% of the applied testosterone dose is absorbed across skin
15.	of average permeability during a 24-hour period.
16.	
17.	The active pharmacologic ingredient in AndroGel™ is testosterone.
18.	Testosterone USP is a white to practically white crystalline powder
19.	chemically described as 17-beta hydroxyandrost-4-en-3-one.
20.	

	PROPOSED LABELING TEXT
21.	 **Testosterone** $C_{19}H_{28}O_2$ MW 288.42
22. 23. 24. 25.	Inactive ingredients in AndroGel™ are ethanol 68.9%, purified water, sodium hydroxide, Carbomer 940 and isopropyl myristate; these ingredients are not pharmacologically active.
26. 27. 28. 29. 30. 31.	**CLINICAL PHARMACOLOGY** AndroGel™ (testosterone gel) delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (298 – 1043 ng/dL) seen in healthy men.
32. 33. 34. 35. 36. 37.	Testosterone--General Androgen Effects: Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic,

	PROPOSED LABELING TEXT
38. 39. 40. 41. 42. 43. 44. 45 46. 47.	chest, and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature, and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis. Hypogonadism is a risk factor for osteoporosis in men.
48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62.	Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

	PROPOSED LABELING TEXT
63. 64. 65. 66. 67. 68. 69. 70. 71.	During exogenous administration of androgens, endogenous testosterone release may be inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH). There is a lack of substantial evidence that androgens are effective in accelerating fracture healing or in shortening post-surgical convalescence.
72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84.	**Pharmacokinetics** Absorption AndroGel™ is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. In a study with the 10 G dose (to deliver 100 mg testosterone), all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady state level by the end of the first 24 hours and are at steady state by the second or third day of dosing.
85. 86. 87.	With single daily applications of AndroGel™, follow-up measurements 30, 90 and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal

	PROPOSED LABELING TEXT
88. 89. 90. 91. 92. 93.	range. Figure 1 summarizes the 24-hour pharmacokinetic profiles of testosterone for patients maintained on 5 G or 10 G of AndroGel™ (to deliver 50 or 100 mg of testosterone, respectively) for 30 days. The average (± SD) daily testosterone concentration produced by AndroGel™ 10 G on Day 30 was 792 (± 294) ng/dL and by AndroGel™ 5 G 566 (262) ng/dL.
94.	 **Figure 1. Mean (±SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying AndroGel™ Once Daily**
95. 96. 97. 98. 99. 100. 101. 102.	When AndroGel™ treatment is discontinued after achieving steady state, serum testosterone levels remain in the normal range for 24 to 48 hours but return to their pretreatment levels by the fifth day after the last application. <u>Distribution</u> Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion

	PROPOSED LABELING TEXT
103.	of testosterone bound to SHBG is not considered biologically active. The
104.	amount of SHBG in the serum and the total testosterone level will determine
105.	the distribution of bioactive and nonbioactive androgen. SHBG-binding
106.	capacity is high in prepubertal children, declines during puberty and
107.	adulthood, and increases again during the later decades of life.
108.	Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains
109.	unbound (free) and the rest is bound to albumin and other proteins.
110.	
111.	Metabolism
112.	There is considerable variation in the half-life of testosterone as reported in
113.	the literature, ranging from ten to 100 minutes.
114.	
115.	Testosterone is metabolized to various 17-keto steroids through two different
116.	pathways. The major active metabolites of testosterone are estradiol and
117.	DHT. DHT binds with greater affinity to SHBG than does testosterone. In
118.	many tissues, the activity of testosterone depends on its reduction to DHT,
119.	which binds to cytosol receptor proteins. The steroid-receptor complex is
120.	transported to the nucleus where it initiates transcription and cellular changes
121.	related to androgen action. In reproductive tissues, DHT is further
122.	metabolized to 3-α and 3-β androstanediol.
123.	
124.	DHT concentrations increased in parallel with testosterone concentrations
125.	during AndroGel™ treatment. After 180 days of treatment, mean DHT
126.	concentrations were within the normal range with 5 G AndroGel™ and were
127.	about 7% above the normal range after a 10 G dose. The mean steady state

	PROPOSED LABELING TEXT
128. 129. 130. 131. 132.	DHT/T ratio during 180 days of AndroGel™ treatment remained within normal limits (as determined by the analytical laboratory involved with this clinical trial) and ranged from 0.23 to 0.29 (5 G/day) and from 0.27 to 0.33 (10 G/day).
133. 134. 135. 136. 137. 138.	Excretion About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.
139. 140. 141. 142. 143. 144.	**Special Populations** In patients treated with AndroGel™, there are no observed differences in the average daily serum testosterone concentration at steady-state based on age, cause of hypogonadism or body mass index. No formal studies were conducted involving patients with renal or hepatic insufficiencies.

	G daily (to deliver 50 mg testosterone), 78 patients to AndroGel™ 10 G daily (to deliver 100 mg testosterone), and 76 patients to a non-scrotal testosterone transdermal system (5 mg daily). The study was double-blind for dose of AndroGel™ but open-label for active control. Patients who were originally randomized to AndroGel™ and who had single-sample serum testosterone levels above or below the normal range on Day 60 were titrated to 7.5 G daily (to deliver 75 mg testosterone) on Day 91. During the Extended Treatment Period (Days 91-180), 51 patients continued on AndroGel™ 5 G daily, 52 patients continued on AndroGel™ 10 G daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received AndroGel™ 7.5 G daily. Mean peak, trough and average serum testosterone concentrations within the normal range (298-1043 ng/dL) were achieved on the first day of treatment with doses of 5 G and 10 G. In patients continuing on AndroGel™ 5 G and 10 G, these mean testosterone levels were maintained within the normal range for the 180-day duration of the study. Figure 2 summarizes the 24-hour pharmacokinetic profiles of testosterone administered as AndroGel™ for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed AndroGel™ treatment.

PROPOSED LABELING TEXT

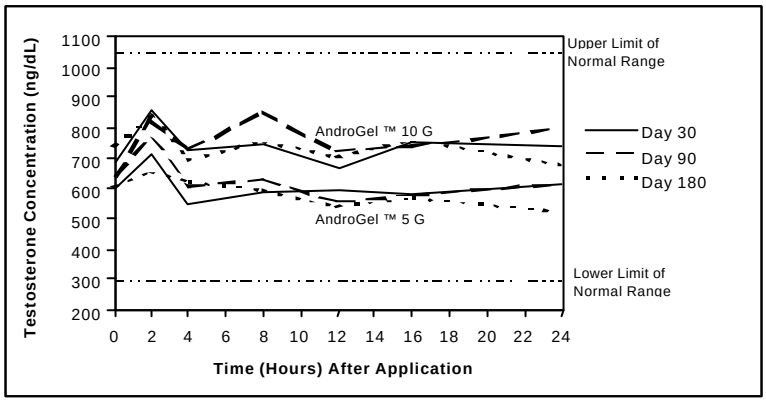


Figure 2. Mean Steady-State Testosterone Concentrations in Patients with Once-Daily AndroGel™ Therapy

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.

	PROPOSED LABELING TEXT
182.	
183. 184. 185. 186. 187. 188. 189.	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™.
190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205.	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. Similar changes were seen after 180 days of treatment and in the group treated with the 7.5 G dose. DHT concentrations increased in parallel with testosterone concentrations at AndroGel™ doses of 5 G/day and 10 G/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with AndroGel™ 5 or 10 G/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of

	PROPOSED LABELING TEXT
206.	(SHBG) decreased very slightly (1 to 11%) during AndroGel™ treatment. In
207.	men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell
208.	in a dose- and time- dependent manner during treatment with AndroGel™.
209.	
210.	
211.	*Potential for testosterone transfer:*
212.	The potential for dermal testosterone transfer following AndroGel™ use was
213.	evaluated in a clinical study between males dosed with AndroGel™ and their
214.	untreated female partners. Two to 12 hours after AndroGel™ (10 G)
215.	application by the male subjects, the couples (N=38 couples) engaged in
216.	daily, 15-minute sessions of vigorous skin-to skin contact so that the female
217.	partners gained maximum exposure to the AndroGel™ application sites.
218.	Under these study conditions, all unprotected female partners had a serum
219.	testosterone concentration > 2 times the baseline value at some time during
220.	the study. When a shirt covered the application site(s), the transfer of
221.	testosterone from the males to the female partners was completely prevented.
222.	
223.	**INDICATIONS AND USAGE**
224.	
225.	AndroGel™ is indicated for replacement therapy in males for conditions
226.	associated with a deficiency or absence of endogenous testosterone:
227.	
228.	1. Primary hypogonadism (congenital or acquired) – testicular failure due to
229.	cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome,
230.	orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from

	PROPOSED LABELING TEXT
231.	alcohol or heavy metals. These men usually have low serum testosterone
232.	levels and gonadotropins (FSH, LH) above the normal range.
233.	
234.	2. Hypogonadotropic hypogonadism (congenital or acquired)--idiopathic
235.	gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency
236.	or pituitary-hypothalamic injury from tumors, trauma, or radiation. These
237.	men have low testosterone serum levels but have gonadotropins in the normal
238.	or low range.
239.	
240.	AndroGel™ has not been clinically evaluated in males under 18 years of age.
241.	
242.	**CONTRAINDICATIONS**
243.	
244.	Androgens are contraindicated in men with carcinoma of the breast or known
245.	or suspected carcinoma of the prostate.
246.	
247.	AndroGel™ is not indicated for use in women, has not been evaluated in
248.	women, and must not be used in women.
249.	
250.	Pregnant women should avoid skin contact with AndroGel™ application sites
251.	in men. Testosterone may cause fetal harm. In the event that unwashed or
252.	unclothed skin to which AndroGel™ has been applied does come in direct
253.	contact with the skin of a pregnant woman, the general area of contact on the
254.	woman should be washed with soap and water as soon as possible. *In vitro*
255.	studies show that residual testosterone is removed from the skin surface by

	PROPOSED LABELING TEXT
256.	washing with soap and water.
257.	AndroGel™ should not be used in patients with known hypersensitivity to
258.	any of its ingredients.
259.	
260.	**WARNINGS**
261.	
262.	1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens
263.	(e.g., methyltestosterone) has been associated with serious hepatic
264.	adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis,
265.	and jaundice). Peliosis hepatitis can be a life-threatening or fatal
266.	complication. Long-term therapy with testosterone enanthate, which
267.	elevates blood levels for prolonged periods, has produced multiple hepatic
268.	adenomas. Testosterone is not known to produce these adverse effects.
269.	
270.	2. Geriatric patients treated with androgens may be at an increased risk for
271.	the development of prostatic hyperplasia and prostatic carcinoma.
272.	
273.	3. Geriatric patients and other patients with clinical or demographic
274.	characteristics that are recognized to be associated with an increased risk
276.	of prostate cancer should be evaluated for the presence of prostate cancer
277.	prior to initiation of testosterone replacement therapy. In men receiving
278.	testosterone replacement therapy, surveillance for prostate cancer should
279.	be consistent with current practices for eugonadal men (see

	PROPOSED LABELING TEXT
280. 281.	PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests).
282. 283. 284. 285. 286. 287. 288 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304.	4. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required. 5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism. 6. The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases. **PRECAUTIONS** Transfer of testosterone to another person can occur when vigorous skin-to-skin contact is made with the application site (see Clinical Studies). The following precautions are recommended to minimize potential transfer of 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).

	PROPOSED LABELING TEXT
305.	• In the event that unwashed or unclothed skin to which AndroGel™ has
306.	been applied does come in direct contact with the skin of another person,
307.	the general area of contact on the other person should be washed with
308.	soap and water as soon as possible. *In vitro* studies show that residual
309.	testosterone is removed from the skin surface by washing with soap and
310.	water.
311.	
312.	Changes in body hair distribution, significant increase in acne, or other signs
313.	of virilization of the female partner should be brought to the attention of a
314.	physician.
315.	
316.	<u>General</u>
317.	The physician should instruct patients to report any of the following:
318.	• Too frequent or persistent erections of the penis.
319.	• Any nausea, vomiting, changes in skin color, or ankle swelling.
320.	• Breathing disturbances, including those associated with sleep.
321.	
322.	<u>Information</u> for Patients
323.	Advise patients to carefully read the information brochure that accompanies
324.	each carton of 30 AndroGel™ single-use packets.
325.	
326.	<u>Advise patients of the following</u>:
327.	• AndroGel™ should not be applied to the scrotum.
328.	• AndroGel™ should be applied once daily to clean dry skin.
329.	• After application of AndroGel™, it is currently unknown for how long

	PROPOSED LABELING TEXT
330.	showering or swimming should be delayed. For optimal absorption of
331.	testosterone, it appears reasonable to wait at least 5-6 hours after
332.	application prior to showering or swimming. Nevertheless, showering or
333.	swimming after just 1 hour should have a minimal effect on the amount of
334.	AndroGel™ absorbed if done very infrequently.
335.	
336.	Laboratory Tests
337.	
338.	1. Hemoglobin and hematocrit levels should be checked periodically (to
339.	detect polycythemia) in patients on long-term androgen therapy.
340.	2. Liver function, prostatic specific antigen, cholesterol, and high-density
341.	lipoprotein should be checked periodically.
342.	3. To ensure proper dosing, serum testosterone concentrations should be
343.	measured (see DOSAGE AND ADMINISTRATION).
344.	
345.	Drug Interactions
346.	Oxyphenbutazone: Concurrent administration of oxyphenbutazone and
347.	androgens may result in elevated serum levels of oxyphenbutazone.
348.	Insulin: In diabetic patients, the metabolic effects of androgens may decrease
349.	blood glucose and, therefore, insulin requirements.
350.	Propranolol: In a published pharmacokinetic study of an injectable
351.	testosterone product, administration of testosterone cypionate led to an
352.	increased clearance of propranolol in the majority of men tested.
353.	Corticosteroids: The concurrent administration of testosterone with ACTH or
354.	corticosteroids may enhance edema formation; thus these drugs should be

	PROPOSED LABELING TEXT
355.	administered cautiously, particularly in patients with cardiac or hepatic
356.	disease.
357.	
358.	Drug/Laboratory Test Interactions
359.	Androgens may decrease levels of thyroxin-binding globulin, resulting in
360.	decreased total T4 serum levels and increased resin uptake of T3 and T4.
361.	Free thyroid hormone levels remain unchanged, however, and there is no
362.	clinical evidence of thyroid dysfunction.
363.	
364.	Carcinogenesis, Mutagenesis, Impairment of Fertility
365.	Animal Data: Testosterone has been tested by subcutaneous injection and
366.	implantation in mice and rats. In mice, the implant induced cervical-uterine
367.	tumors, which metastasized in some cases. There is suggestive evidence that
368.	injection of testosterone into some strains of female mice increases their
369.	susceptibility to hepatoma. Testosterone is also known to increase the
370.	number of tumors and decrease the degree of differentiation of chemically
371.	induced carcinomas of the liver in rats.
372.	
373.	Human Data: There are rare reports of hepatocellular carcinoma in patients
374.	receiving long-term oral therapy with androgens in high doses. Withdrawal of
375.	the drugs did not lead to regression of the tumors in all cases.
376.	Geriatric patients treated with androgens may be at an increased risk for the
377.	development of prostatic hyperplasia and prostatic carcinoma.
378.	
379.	Geriatric patients and other patients with clinical or demographic

	PROPOSED LABELING TEXT
380. 381. 382.	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.
383. 384.	In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men.
385. 386.	Pregnancy Category X (see Contraindications)--Teratogenic Effects: AndroGel™ is not indicated for women and must not be used in women.
387. 388.	Nursing Mothers: AndroGel™ is not indicated for women and must not be used in women.
389.	
390. 391.	Pediatric Use: Safety and efficacy of AndroGel™ in pediatric patients have not been established.
392.	
393.	**ADVERSE REACTIONS**
394.	
395. 396. 397. 398.	In a controlled clinical study, 154 patients were treated with AndroGel™ for up to 6 months (see Clinical Studies). Adverse Events possibly, probably or definitely related to the use of AndroGel™ and reported by 1% of the patients are listed in Table 2.
399. 400.	

PROPOSED LABELING TEXT

Table 2. Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel™ in the Controlled Clinical Trial

Adverse Event	5 G	7.5 G	10 G
Acne	1%	3%	8%
Alopecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder	3%	0%	0%

401. * *Lab test abnormal* occurred in nine patients with one or more of the
402. following events: elevated hemoglobin or hematocrit, hyperlipidemia,
403. elevated triglycerides, hypokalemia, decreased HDL, elevated glucose,
404. elevated creatinine, or elevated total bilirubin.
405. ** *Prostate disorders* included five patients with enlarged prostate, one
406. patient with BPH, and one patient with elevated PSA results.
407.
408. The following adverse events possibly related to the use of AndroGel™
409. occurred in fewer than 1% of patients: amnesia, anxiety, discolored hair,
410. dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis
411. disorder, peripheral edema, sweating, and vasodilation.
412. In this clinical trial of AndroGel™, skin reactions at the site of application

	PROPOSED LABELING TEXT
413. 414. 415. 416. 417.	were occasionally reported with AndroGel™, but none was severe enough to require treatment or discontinuation of drug.
418. 419. 420. 421. 422. 423. 424.	Six (4%) patients in this trial had adverse events that led to discontinuation of AndroGel™. These events included the following: cerebral hemorrhage, convulsion (neither of which were considered related to AndroGel™ administration), depression, sadness, memory loss, elevated prostate specific antigen and hypertension. No AndroGel™ patients discontinued due to skin reactions.
425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436.	In an uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with AndroGel™; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other. Among 17 patients in foreign clinical studies there was 1 instance each of acne, erythema and benign prostate adenoma associated with a 2.5% testosterone gel formulation applied dermally. One hundred six (106) patients have received AndroGel™ for up to 12 months in a long-term follow-up study for patients who completed the controlled clinical trial. The preliminary safety results from this study are consistent with those reported for the controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or definitely related to the use of AndroGel™ and reported by at least 1% of the total number of

PROPOSED LABELING TEXT

patients during long-term exposure to AndroGel™.

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

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

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

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

DRUG ABUSE AND DEPENDENCE

	PROPOSED LABELING TEXT
452. 453. 454. 455.	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.
456. 457. 458. 459. 460. 461.	**OVERDOSAGE** There is one report of acute overdosage by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.
462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472.	**DOSAGE AND ADMINISTRATION** The recommended starting dose of AndroGel™ 1% is 5 G (to deliver 50 mg of testosterone) applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after AndroGel™ has been applied. Do not apply AndroGel™ to the genitals.

PROPOSED LABELING TEXT

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

HOW SUPPLIED

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

AndroGel™ is supplied in unit-dose aluminum foil packets in cartons of 30. Each packet contains 2.5 G or 5.0 G of gel to deliver 25 mg or 50 mg of testosterone, respectively, and is supplied as follows:

NDC Number	Strength	Package Size
0051-8425-30	1% (25 mg)	30 packets: 2.5 G per packet
0051-8450-30	1% (50 mg)	30 packets: 5 G per packet

Storage

	PROPOSED LABELING TEXT
495.	Store at controlled room temperature 20-25°C (68-77°F) [see USP].
496.	
497.	Disposal
498.	Used AndroGel™ packets should be discarded in household trash in a
499.	manner that prevents accidental application or ingestion by children or pets.
500.	
501.	Rx Only
502.	
503.	Manufactured by Laboratoires Besins Iscovesco
504.	Montrouge, France
505.	
506.	For:
507.	
508.	Unimed Pharmaceuticals, Inc.
509.	Buffalo Grove, IL 60089-1864, USA