# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-015**

# APPROVED DRAFT LABELING

| | 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. | |

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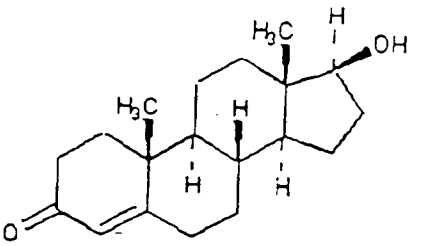
| 21. |  Testosterone $C_{19}H_{28}O_2$ MW 288.42 |
| 22. 23. 24. 25. | Inactive ingredients in AndroGel™ are ethanol 68.9%, purified water, sodium hydroxide, Carbomer 940 and isopropyl myristate; these ingredients are not pharmacologically active. |
| 26. 27. 28. 29. 30. 31. | **CLINICAL PHARMACOLOGY**<br><br>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:<br>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, |

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| 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.<br><br>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. |

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

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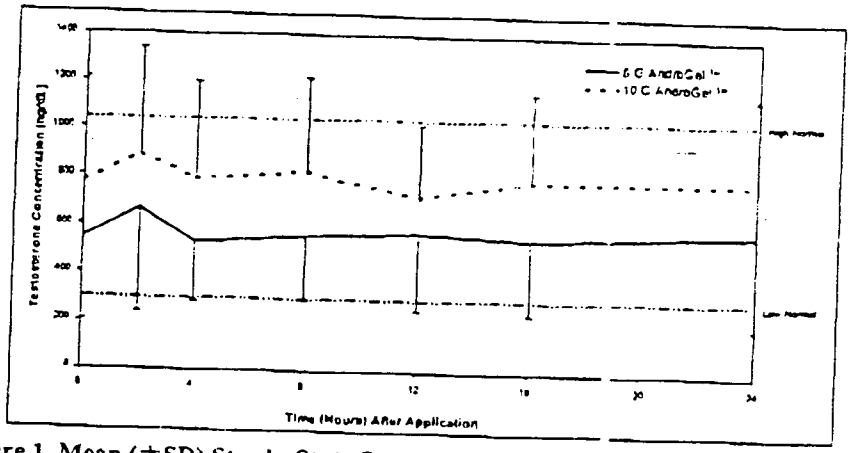
| 88. 89. 90. 91. 92. 93. | range. Figure 1 summarizes the 24-hour pharmacokinetic profiles of testosterone for patients maintained on 5 G or 10 G of AndroGel™ (to deliver 50 or 100 mg of testosterone, respectively) for 30 days. The average (± SD) daily testosterone concentration produced by AndroGel™ 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. | 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.<br><br><u>Distribution</u><br>Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone |

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| 102. | easily dissociates from albumin and is presumed to be bioactive. The portion |
| 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 |

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| 127. 128. 129. 130. 131. 132. | about 7% above the normal range after a 10 G dose. The mean steady state 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<br>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**<br>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. |

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| 145. | **Clinical Studies** |
| 146. | AndroGel™ 1% was evaluated in a multicenter, randomized, parallel-group, |
| 147. | active-controlled, 180-day trial in 227 hypogonadal men. The study was |
| 148. | conducted in 2 phases. During the Initial Treatment Period (Days 1-90), 73 |
| 149. | patients were randomized to AndroGel™ 5 G daily (to deliver 50 mg |
| 150. | testosterone), 78 patients to AndroGel™ 10 G daily (to deliver 100 mg |
| 151. | testosterone), and 76 patients to a non-scrotal testosterone transdermal system |
| 152. | (5 mg daily). The study was double-blind for dose of AndroGel™ but open- |
| 153. | label for active control. Patients who were originally randomized to |
| 154. | AndroGel™ and who had single-sample serum testosterone levels above or |
| 155. | below the normal range on Day 60 were titrated to 7.5 G daily (to deliver 75 |
| 156. | mg testosterone) on Day 91. During the Extended Treatment Period (Days |
| 157. | 91-180), 51 patients continued on AndroGel™ 5 G daily, 52 patients |
| 158. | continued on AndroGel™ 10 G daily, 41 patients continued on a non-scrotal |
| 159. | testosterone transdermal system (5 mg daily), and 40 patients received |
| 160. | AndroGel™ 7.5 G daily. |
| 161. | |
| 162. | Mean peak, trough and average serum testosterone concentrations within the |
| 163. | normal range (298-1043 ng/dL) were achieved on the first day of treatment |
| 164. | with doses of 5 G and 10 G. In patients continuing on AndroGel™ 5 G and |
| 165. | 10 G, these mean testosterone levels were maintained within the normal range |
| 166. | for the 180-day duration of the study. Figure 2 summarizes the 24-hour |
| 167. | pharmacokinetic profiles of testosterone administered as AndroGel™ for 30, |
| 168. | 90 and 180 days. Testosterone concentrations were maintained as long as the |
| 169. | patient continued to properly apply the prescribed AndroGel™ treatment. |

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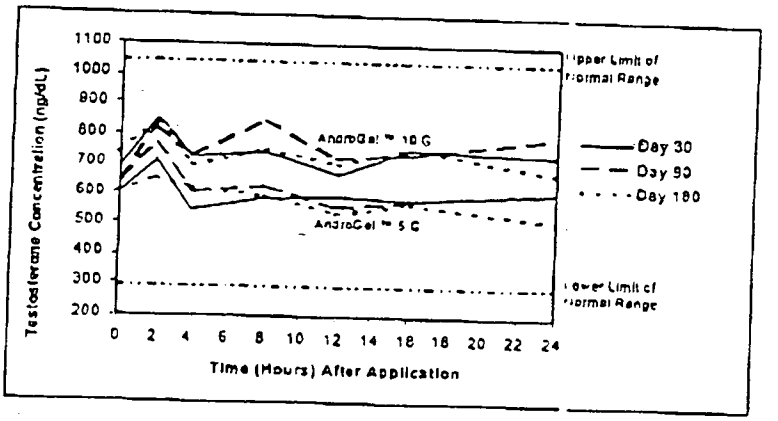
| 170. | |
| 171. |  |



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

172. Table 1 summarizes the mean testosterone concentrations on Treatment Day
173. 180 for patients receiving 5 G, 7.5 G, or 10 G of AndroGel™. The 7.5 G
174. dose produced mean concentrations intermediate to those produced by 5 G
175. and 10 G of AndroGel™.
176.
177.

**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 |

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

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| 181.<br>182. | |
| 183.<br>184.<br>185.<br>186.<br>187.<br>188.<br>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.<br>191.<br>192.<br>193.<br>194.<br>195.<br>196.<br>197.<br>198.<br>199.<br>200.<br>201.<br>202.<br>203.<br>204. | 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.<br><br>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 |

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| 205. | remained within the normal range for eugonadal men. Serum levels of |
| 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, |

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| 230. | orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from |
| 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* |

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| 255.<br>256. | studies show that residual testosterone is removed from the skin surface by washing with soap and water. |
| 257.<br>258.<br>259. | AndroGel™ should not be used in patients with known hypersensitivity to any of its ingredients. |
| 260.<br>261. | **WARNINGS** |
| 262.<br>263.<br>264.<br>265.<br>266.<br>267.<br>268.<br>269. | 1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone is not known to produce these adverse effects. |
| 270.<br>271.<br>272. | 2. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma. |
| 273.<br>274.<br>276.<br>277.<br>278. | 3. 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 |

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| 279.<br>280.<br>281. | be consistent with current practices for eugonadal men (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests). |
| 282.<br>283.<br>284.<br>285.<br>286. | 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. |
| 287.<br>288<br>289. | 5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism. |
| 290.<br>291.<br>292.<br>293.<br>294. | 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. |
| 295.<br>296. | **PRECAUTIONS** |
| 297.<br>298.<br>299.<br>300. | 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: |
| 301.<br>302. | • Patients should wash their hands immediately with soap and water after application of AndroGel™. |
| 303. | • Patients should cover the application site(s) with clothing after the gel has |

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| 304. | dried (e.g. a shirt). |
| 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. | General |
| 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. | Information for Patients |
| 323. | Advise patients to carefully read the information brochure that accompanies |
| 324. | each carton of 30 AndroGel™ single-use packets. |
| 325. | |
| 326. | Advise patients of the following: |
| 327. | • AndroGel™ should not be applied to the scrotum. |
| 328. | • AndroGel™ should be applied once daily to clean dry skin. |

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| 329. | • After application of AndroGel™, it is currently unknown for how long |
| 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 |

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| 354. | corticosteroids may enhance edema formation; thus these drugs should be |
| 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. | |

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| 379. | Geriatric patients and other patients with clinical or demographic |
| 380. | characteristics that are recognized to be associated with an increased risk of |
| 381. | prostate cancer should be evaluated for the presence of prostate cancer prior |
| 382. | to initiation of testosterone replacement therapy. |
| 383. | In men receiving testosterone replacement therapy, surveillance for prostate |
| 384. | cancer should be consistent with current practices for eugonadal men. |
| 385. | Pregnancy Category X (see Contraindications)--Teratogenic Effects: |
| 386. | AndroGel™ is not indicated for women and must not be used in women. |
| 387. | Nursing Mothers: AndroGel™ is not indicated for women and must not be |
| 388. | used in women. |
| 389. | |
| 390. | Pediatric Use: Safety and efficacy of AndroGel™ in pediatric patients have |
| 391. | not been established. |
| 392. | |
| 393. | **ADVERSE REACTIONS** |
| 394. | |
| 395. | In a controlled clinical study, 154 patients were treated with AndroGel™ for |
| 396. | up to 6 months (see Clinical Studies). Adverse Events possibly, probably or |
| 397. | definitely related to the use of AndroGel™ and reported by ≥ 1% of the |
| 398. | patients are listed in Table 2. |
| 399. | |
| 400. | |

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**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

| | PROPOSED LABELING TEXT |
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| 412.<br>413.<br>414.<br>415.<br>416.<br>417. | In this clinical trial of AndroGel™, skin reactions at the site of application were occasionally reported with AndroGel™, but none was severe enough to require treatment or discontinuation of drug. |
| 418.<br>419.<br>420.<br>421.<br>422.<br>423.<br>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.<br>426.<br>427.<br>428.<br>429.<br>430.<br>431.<br>432.<br>433.<br>434.<br>435. | 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.<br>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 |

**PROPOSED LABELING TEXT**

the use of AndroGel™ and reported by at least 1% of the total number of 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**

| | Dose of AndroGel™ | | |
|---|---|---|---|
| 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.

| | PROPOSED LABELING TEXT |
|---|---|
| 451. | **DRUG ABUSE AND DEPENDENCE** |
| 452. | |
| 453. | AndroGel™ contains testosterone, a Schedule III controlled substance as |
| 454. | defined by the Anabolic Steroids Control Act. |
| 455. | Oral ingestion of AndroGel™ will not result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism. |
| 456. | **OVERDOSAGE** |
| 457. | |
| 458. | There is one report of acute overdosage by injection of testosterone |
| 459. | enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a |
| 460. | cerebrovascular accident. |
| 461. | |
| 462. | **DOSAGE AND ADMINISTRATION** |
| 463. | |
| 464. | The recommended starting dose of AndroGel™ 1% is 5 G (to deliver 50 mg |
| 465. | of testosterone) applied once daily (preferably in the morning) to clean, dry, |
| 466. | intact skin of the shoulders and upper arms and/or abdomen. Upon opening |
| 467. | the packet(s), the entire contents should be squeezed into the palm of the hand |
| 468. | and immediately applied to the application sites. Application sites should be |
| 469. | allowed to dry for a few minutes prior to dressing. Hands should be washed |
| 470. | with soap and water after AndroGel™ has been applied. |
| 471. | |

| | PROPOSED LABELING TEXT |
|---|---|
| 472. | Do not apply AndroGel™ to the genitals. |
| 473. | |
| 474. | Serum testosterone levels should be measured approximately 14 days after |
| 475. | initiation of therapy to ensure proper dosing. If the serum testosterone |
| 476. | concentration is below the normal range, or if the desired clinical response is |
| 477. | not achieved, the daily AndroGel™ 1% dose may be increased from 5 G to |
| 478. | 7.5 G and from 7.5 G to 10 G as instructed by the physician. |
| 479. | |
| 480. | **HOW SUPPLIED** |
| 481. | |
| 482. | AndroGel™ contains testosterone, a Schedule III controlled substance as |
| 483. | defined by the Anabolic Steroids Control Act. |
| 484. | |
| 485. | AndroGel™ is supplied in unit-dose aluminum foil packets in cartons of 30. |
| 486. | Each packet contains 2.5 G or 5.0 G of gel to deliver 25 mg or 50 mg of |
| 487. | testosterone, respectively, and is supplied as follows: |
| 488. | |

| 489. | NDC Number | Strength | Package Size |
|---|---|---|---|
| 490. | 0051-8425-30 | 1% (25 mg) | 30 packets: 2.5 G per packet |
| 491. | 0051-8450-30 | 1% (50 mg) | 30 packets: 5 G per packet |
| 492. | | | |
| 493. | | | |

| | PROPOSED LABELING TEXT |
|---|---|
| 494. | Storage |
| 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 |

# Patient Information and Instructions for Using ANDROGEL™ 1% (testosterone gel) C-III

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

## What is ANDROGEL?

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

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

## Who should not take ANDROGEL?

AndroGel **must not be used by women** or by those individuals with known hypersensitivity to any of its components. Pregnant women should avoid skin contact with AndroGel application sites in men. The active ingredient in AndroGel is testosterone. (See "Inactive Ingredients" at the end of this leaflet for a list of the other ingredients.) Testosterone may cause fetal harm.

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

- prostate cancer (if your doctor knows for sure or suspects it)
- breast cancer (a rare condition for men)
- heart, kidney, or liver disease
- difficulty in urinating due to an enlarged prostate

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

## How should I use ANDROGEL?

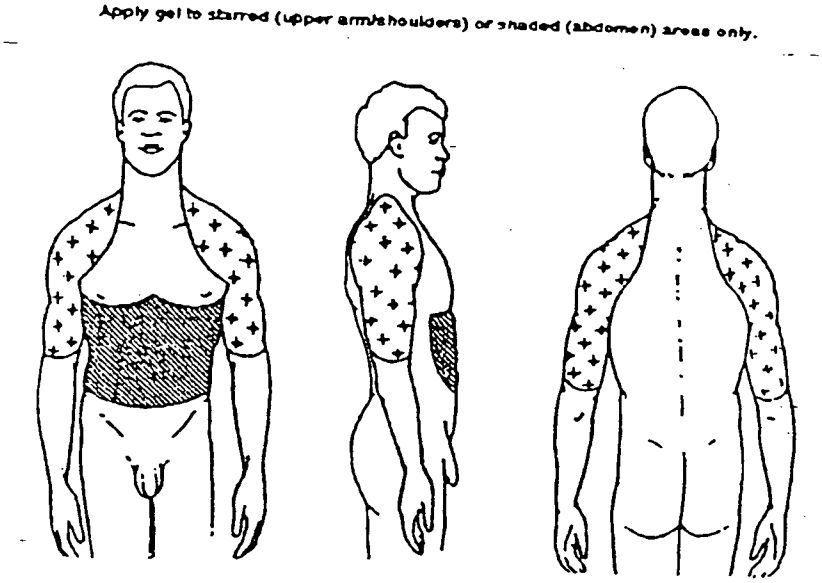
It is important that you read and follow these directions on how to use AndroGel properly.

1. **Apply AndroGel at the same time (preferably every morning).** You should apply the contents of one (1) packet of gel every morning. If you take a bath or shower in the morning, use AndroGel after your bath or shower. Your doctor may tell you to use more than one packet at a time.

2. **Be sure your skin is completely dry.**

3. **Open the packet.** Open one AndroGel aluminum foil packet by folding the top edge and tearing open the packet.

4. **Remove the contents from the packet. Squeeze the entire contents into the palm of your hand. Squeeze from the bottom of the packet toward the top. If you like, you can squeeze out half (1/2) of the contents of the packet at a time and then squeeze out the second half after you have applied the first half, following the directions below.**




5. **Apply AndroGel only to your abdomen (stomach area), shoulders, or upper arms.** In this way your body will absorb the right amount of testosterone. **Never apply AndroGel to your genitals (penis and scrotum) or to damaged skin.** Apply AndroGel only to healthy, normal skin. Avoid skin with open sores, wounds, or irritation. Use a circular motion to rub the gel for several seconds.

6. **Wash your hands with soap and water right away after application.** Wash your hands right away to reduce the chance that the medicine will spread from your hands to other people.

7. **Let AndroGel dry for a few minutes before you dress.** This prevents your clothing from wiping the gel off your skin. It ensures that your body will absorb the correct amount of testosterone.

8. **Wait 5 to 6 hours before showering or swimming.** To ensure that the greatest amount of AndroGel is absorbed into your system, you should wait 5 to 6 hours after application before showering or swimming. Once in a while, you may shower or swim as soon as 1 hour after applying AndroGel. If done infrequently, this will have little effect on the amount of AndroGel that is absorbed by your body.

9. **Maintain normal activities.** Once your hands are washed and the application site is covered with clothing, there is little risk of transferring testosterone to someone else's skin due to bodily contact. If, however, you expect direct skin contact with someone else, you should wash your application site with soap and water before that encounter. This will reduce the chance that the medicine will transfer to the other person.

**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.**

**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
- any side effect that concerns you

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

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

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

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

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

Manufactured by: Laboratoires Besins Iscovesco
Montrouge, France
For Unimed Pharmaceuticals, Inc.
Buffalo Grove, IL 60089