

PRESCRIBING INFORMATION

AVODART[®]

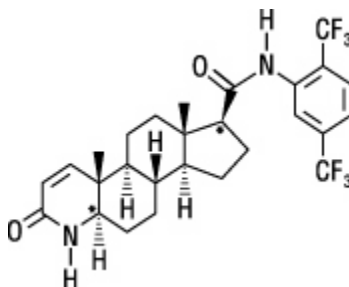
(dutasteride)

Soft Gelatin Capsules

DESCRIPTION

AVODART (dutasteride) is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5 α -reductase (5AR), an intracellular enzyme that converts testosterone to 5 α -dihydrotestosterone (DHT).

Dutasteride is chemically designated as (5 α ,17 β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is C₂₇H₃₀F₆N₂O₂, representing a molecular weight of 528.5 with the following structural formula:



Dutasteride is a white to pale yellow powder with a melting point of 242° to 250°C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL), and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

AVODART Soft Gelatin Capsules for oral administration contain 0.5 mg of the active ingredient dutasteride in yellow capsules with red print. Each capsule contains 0.5 mg of dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified BSE-free bovine sources), glycerin, and ferric oxide (yellow). The soft gelatin capsules are printed with edible red ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Mechanism of Action: Dutasteride inhibits the conversion of testosterone to 5 α -dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5 α -reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5 α -reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has

33 been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not
34 bind to the human androgen receptor.

35 **Effect on 5 α -Dihydrotestosterone and Testosterone:** The maximum effect of daily
36 doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to
37 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT
38 concentrations were reduced by 85% and 90%, respectively. In patients with benign prostatic
39 hyperplasia (BPH) treated with dutasteride 0.5 mg/day for 4 years, the median decrease in serum
40 DHT was 94% at 1 year, 93% at 2 years, and 95% at both 3 and 4 years. The median increase in
41 serum testosterone was 19% at both 1 and 2 years, 26% at 3 years, and 22% at 4 years, but the
42 mean and median levels remained within the physiologic range.

43 In patients with BPH treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior
44 to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were
45 significantly lower in the dutasteride group compared with placebo (784 and 5,793 pg/g,
46 respectively, $p < 0.001$). Mean prostatic tissue concentrations of testosterone were significantly
47 higher in the dutasteride group compared with placebo (2,073 and 93 pg/g, respectively,
48 $p < 0.001$).

49 Adult males with genetically inherited type 2 5 α -reductase deficiency also have decreased
50 DHT levels. These 5 α -reductase deficient males have a small prostate gland throughout life and
51 do not develop BPH. Except for the associated urogenital defects present at birth, no other
52 clinical abnormalities related to 5 α -reductase deficiency have been observed in these individuals.

53 **Other Effects:** Plasma lipid panel and bone mineral density were evaluated following
54 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone
55 mineral density as measured by dual energy x-ray absorptiometry (DEXA) compared with either
56 placebo or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low density
57 lipoproteins, high density lipoproteins, and triglycerides) was unaffected by dutasteride. No
58 clinically significant changes in adrenal hormone responses to ACTH stimulation were observed
59 in a subset population ($n = 13$) of the 1-year healthy volunteer study.

60 **Pharmacokinetics: Absorption:** Following administration of a single 0.5-mg dose of a soft
61 gelatin capsule, time to peak serum concentrations (T_{max}) of dutasteride occurs within 2 to
62 3 hours. Absolute bioavailability in 5 healthy subjects is approximately 60% (range, 40% to
63 94%). When the drug is administered with food, the maximum serum concentrations were
64 reduced by 10% to 15%. This reduction is of no clinical significance.

65 **Distribution:** Pharmacokinetic data following single and repeat oral doses show that
66 dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to
67 plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%).

68 In a study of healthy subjects ($n = 26$) receiving dutasteride 0.5 mg/day for 12 months, semen
69 dutasteride concentrations averaged 3.4 ng/mL (range, 0.4 to 14 ng/mL) at 12 months and,
70 similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months
71 11.5% of serum dutasteride concentrations partitioned into semen.

72 **Metabolism and Elimination:** Dutasteride is extensively metabolized in humans. In vitro
73 studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both
74 of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride, and the
75 6,4'-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was
76 formed by CYP3A4. Dutasteride is not metabolized in vitro by human cytochrome P450
77 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and
78 CYP2E1. In human serum following dosing to steady state, unchanged dutasteride, 3 major
79 metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride), and
80 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass
81 spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl
82 additions in the 6 and 15 positions is not known. In vitro, the 4'-hydroxydutasteride and
83 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of
84 human 5AR. The activity of 6 β -hydroxydutasteride is comparable to that of dutasteride.

85 Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there was
86 approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related
87 metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine
88 (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range, 5% to 97%).

89 The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state. The
90 average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for
91 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state
92 concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of
93 dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to
94 6 months after discontinuation of treatment.

95 **Special Populations: Pediatric:** Dutasteride pharmacokinetics have not been investigated in
96 subjects younger than 18 years.

97 **Geriatric:** No dose adjustment is necessary in the elderly. The pharmacokinetics and
98 pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects aged between 24
99 and 87 years following administration of a single 5-mg dose of dutasteride. In this single-dose
100 study, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to
101 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in
102 men older than 70 years). Of 2,167 men treated with dutasteride in the 3 pivotal studies, 60%
103 were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy
104 were observed between these patients and younger patients.

105 **Gender:** AVODART is not indicated for use in women (see WARNINGS and
106 PRECAUTIONS). The pharmacokinetics of dutasteride in women have not been studied.

107 **Race:** The effect of race on dutasteride pharmacokinetics has not been studied.

108 **Renal Impairment:** The effect of renal impairment on dutasteride pharmacokinetics has not
109 been studied. However, less than 0.1% of a steady-state 0.5-mg dose of dutasteride is recovered
110 in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

111 **Hepatic Impairment:** The effect of hepatic impairment on dutasteride pharmacokinetics has
112 not been studied. Because dutasteride is extensively metabolized, exposure could be higher in
113 hepatically impaired patients (see PRECAUTIONS: Use in Hepatic Impairment).

114 **Drug Interactions:** In vitro drug metabolism studies reveal that dutasteride is metabolized by
115 the human cytochrome P450 isoenzymes CYP3A4 and CYP3A5. In a human mass balance
116 analysis (n = 8), dutasteride was extensively metabolized. Less than 20% of the dose was
117 excreted unchanged in the feces. No clinical drug interaction studies have been performed to
118 evaluate the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics. However,
119 based on the in vitro data, blood concentrations of dutasteride may increase in the presence of
120 inhibitors of CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine,
121 troleandomycin, and ciprofloxacin. Dutasteride is not metabolized in vitro by human cytochrome
122 P450 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and
123 CYP2E1.

124 Clinical drug interaction studies have shown no pharmacokinetic or pharmacodynamic
125 interactions between dutasteride and tamsulosin, terazosin, warfarin, digoxin, and
126 cholestyramine (see PRECAUTIONS: Drug Interactions).

127 Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human
128 cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a
129 concentration of 1,000 ng/mL, 25 times greater than steady-state serum concentrations in
130 humans.

131 **CLINICAL STUDIES**

132 Dutasteride 0.5 mg/day (n = 2,167) or placebo (n = 2,158) was evaluated in male subjects
133 with BPH in three 2-year multicenter, placebo-controlled, double-blind studies, each with 2-year
134 open-label extensions (n = 2,340). More than 90% of the study population was Caucasian.
135 Subjects were at least 50 years of age with a serum prostate-specific antigen (PSA) ≥ 1.5 ng/mL
136 and < 10 ng/mL and BPH diagnosed by medical history and physical examination, including
137 enlarged prostate (≥ 30 cc) and BPH symptoms that were moderate to severe according to the
138 American Urological Association Symptom Index (AUA-SI). Most of the 4,325 subjects
139 randomly assigned to receive either dutasteride or placebo completed 2 years of double-blind
140 treatment (70% and 67%, respectively). Most of the 2,340 subjects in the study extensions
141 completed 2 additional years of open-label treatment (71%).

142 **Effect on Symptom Scores:** Symptoms were quantified using the AUA-SI, a questionnaire
143 that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak
144 stream, straining, and nocturia) by rating on a 0 to 5 scale for a total possible score of 35. The
145 baseline AUA-SI score across the 3 studies was approximately 17 units in both treatment groups.

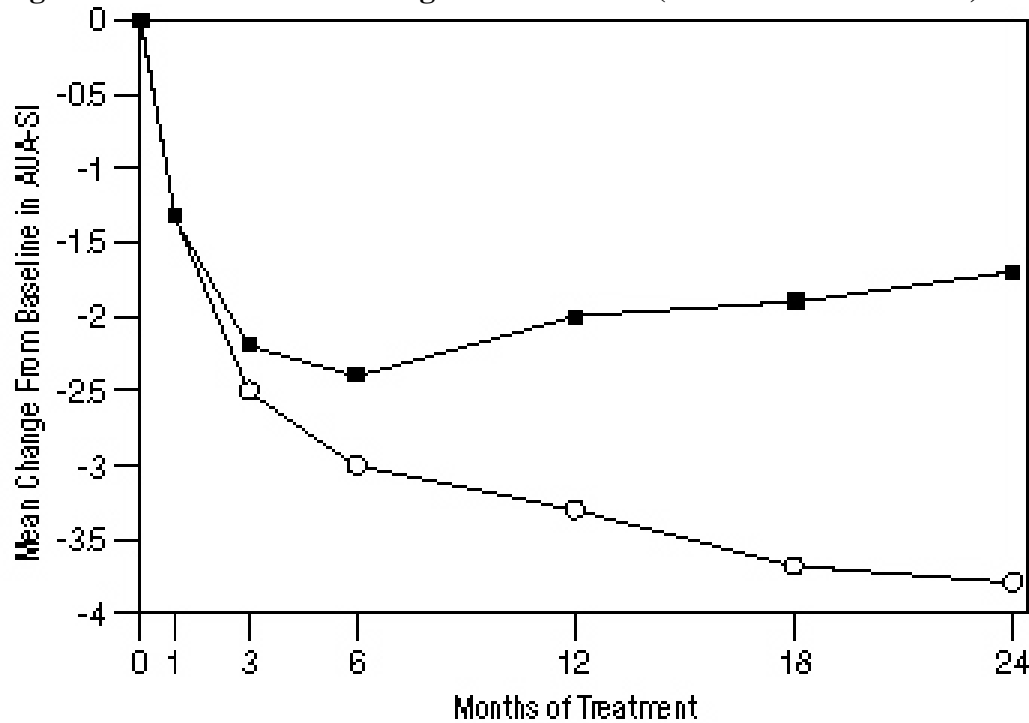
146 Subjects receiving dutasteride achieved statistically significant improvement in symptoms
147 versus placebo by Month 3 in one study and by Month 12 in the other 2 pivotal studies. At
148 Month 12, the mean decrease from baseline in AUA-SI symptom scores across the 3 studies
149 pooled was -3.3 units for dutasteride and -2.0 units for placebo with a mean difference between

150 the 2 treatment groups of -1.3 (range, -1.1 to -1.5 units in each of the 3 studies, $p < 0.001$) and was
 151 consistent across the 3 studies. At Month 24, the mean decrease from baseline was -3.8 units for
 152 dutasteride and -1.7 units for placebo with a mean difference of -2.1 (range, -1.9 to -2.2 units in
 153 each of the 3 studies, $p < 0.001$). See Figure 1. The improvement in BPH symptoms seen during
 154 the first 2 years of double-blind treatment was maintained throughout an additional 2 years of
 155 open-label extension studies.

156 These studies were prospectively designed to evaluate effects on symptoms based on prostate
 157 size at baseline. In men with prostate volumes ≥ 40 cc, the mean decrease was -3.8 units for
 158 dutasteride and -1.6 units for placebo, with a mean difference between the 2 treatment groups of
 159 -2.2 at Month 24. In men with prostate volumes < 40 cc, the mean decrease was -3.7 units for
 160 dutasteride and -2.2 units for placebo, with a mean difference between the 2 treatment groups of
 161 -1.5 at Month 24.

162

163 **Figure 1. AUA-SI Score* Change from Baseline (Pivotal Studies Pooled)**



164 ■ Placebo n = 2,122 n = 2,123 n = 2,123 n = 2,123
 165 □ Dutasteride n = 2,122 n = 2,122 n = 2,122 n = 2,122

*AUA-SI score ranges from 0 to 35.

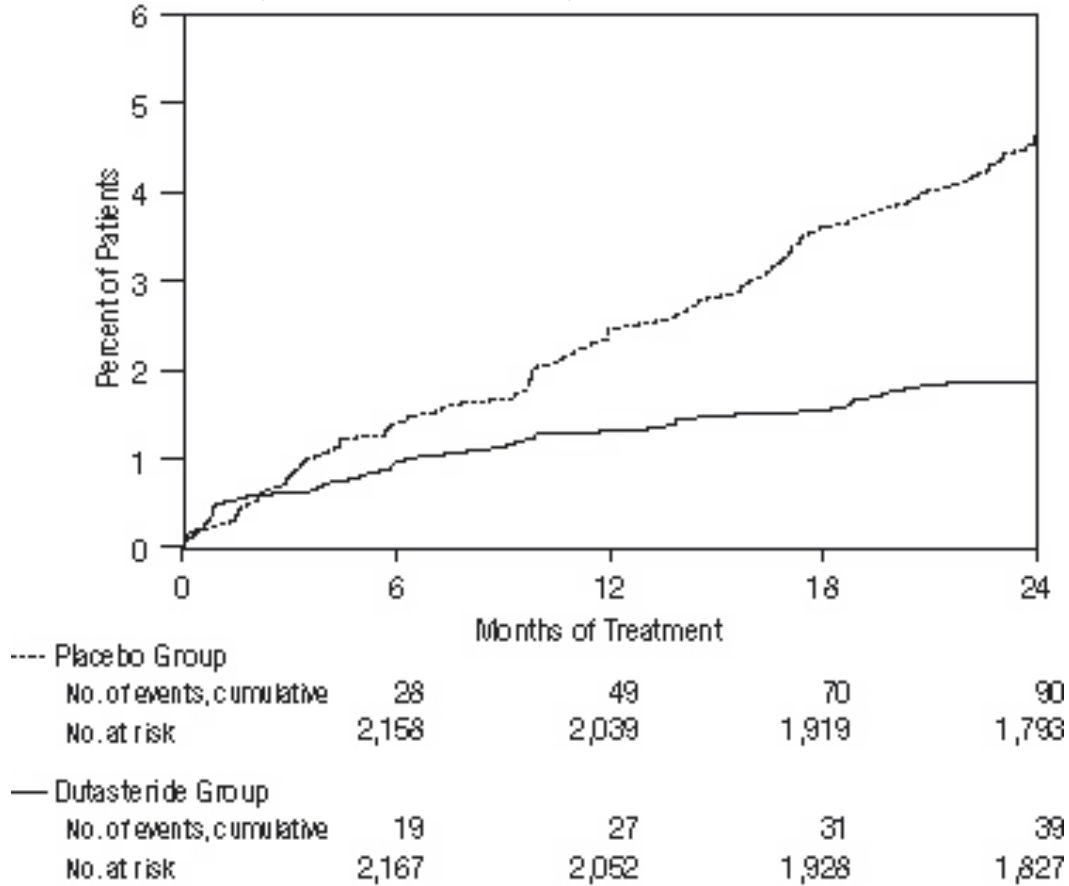
166

167 **Effect on Acute Urinary Retention and the Need for Surgery:** Efficacy was also
 168 assessed after 2 years of treatment by the incidence of acute urinary retention (AUR) requiring
 169 catheterization and BPH-related urological surgical intervention. Compared with placebo,
 170 AVODART was associated with a statistically significantly lower incidence of AUR (1.8% for
 171 AVODART vs. 4.2% for placebo, $p < 0.001$; 57% reduction in risk, 95% CI: [38-71%]) and with

172 a statistically significantly lower incidence of surgery (2.2% for AVODART vs. 4.1% for
 173 placebo, $p < 0.001$; 48% reduction in risk, 95% CI: [26-63%]). See Figures 2 and 3.

174

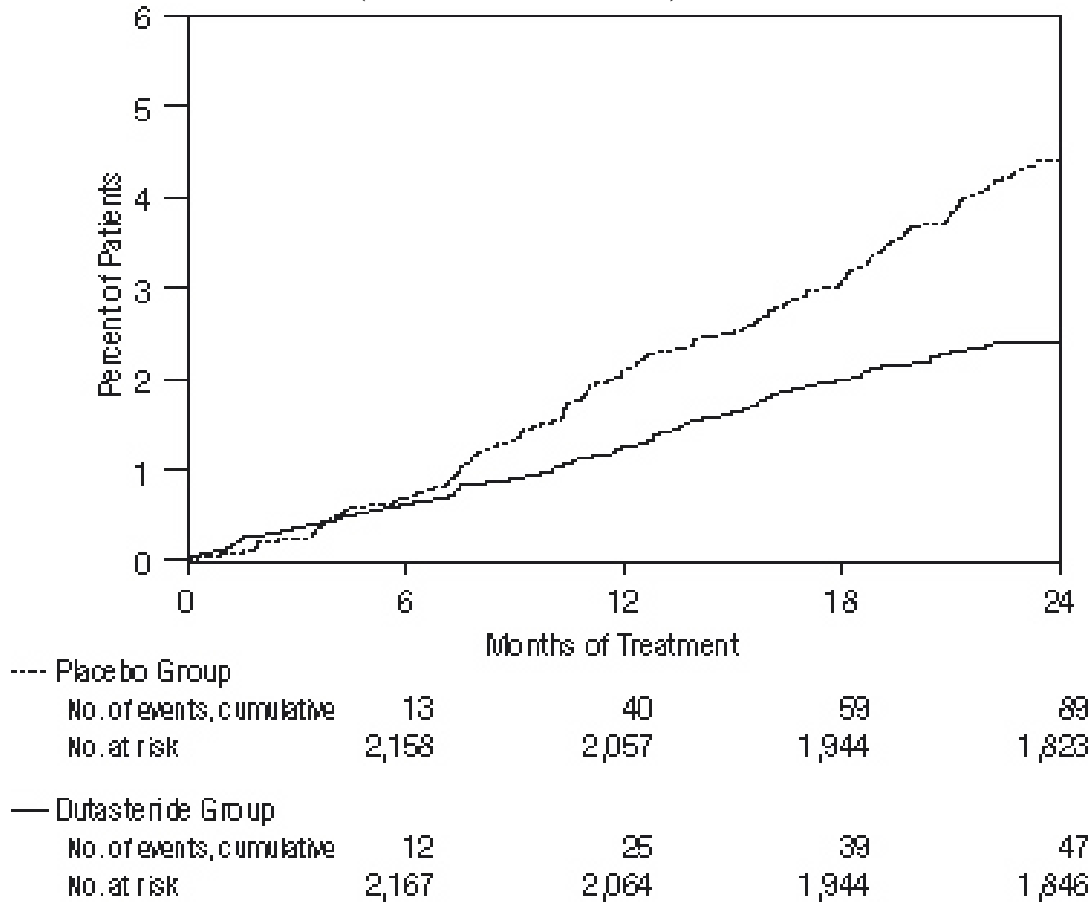
175 **Figure 2. Percent of Subjects Developing Acute Urinary Retention Over a**
 176 **24-Month Period (Pivotal Studies Pooled)**



177

178

179 **Figure 3. Percent of Subjects Having Surgery for Benign Prostatic Hyperplasia**
 180 **Over a 24-Month Period (Pivotal Studies Pooled)**



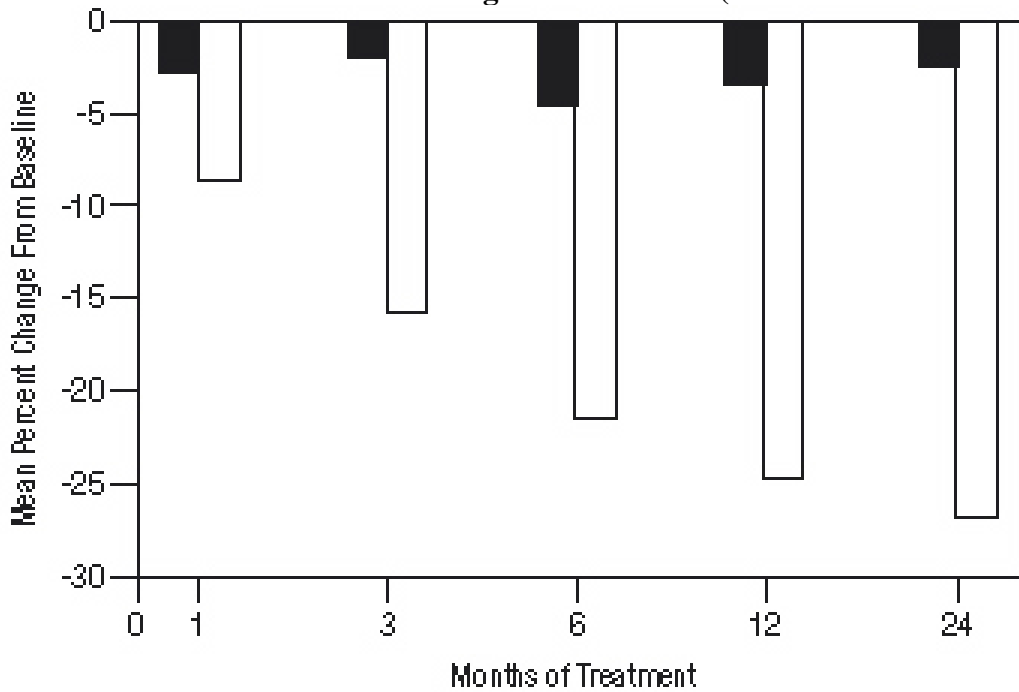
181
 182

183 **Effect on Prostate Volume:** A prostate volume of at least 30 cc measured by transrectal
 184 ultrasound was required for study entry. The mean prostate volume at study entry was
 185 approximately 54 cc.

186 Statistically significant differences (dutasteride vs. placebo) were noted at the earliest post-
 187 treatment prostate volume measurement in each study (Month 1, Month 3, or Month 6) and
 188 continued through Month 24. At Month 12, the mean percent change in prostate volume across
 189 the 3 studies pooled was -24.7% for dutasteride and -3.4% for placebo; the mean difference
 190 (dutasteride minus placebo) was -21.3% (range, -21.0% to -21.6% in each of the 3 studies,
 191 $p < 0.001$). At Month 24, the mean percent change in prostate volume across the 3 studies pooled
 192 was -26.7% for dutasteride and -2.2% for placebo with a mean difference of -24.5% (range,
 193 -24.0% to -25.1% in each of the 3 studies, $p < 0.001$). See Figure 4. The reduction in prostate
 194 volume seen during the first 2 years of double-blind treatment was maintained throughout an
 195 additional 2 years of open-label extension studies.

196

197 **Figure 4. Prostate Volume Percent Change from Baseline (Pivotal Studies Pooled)**



■ Placebo	n = 704	n = 645	n = 2,033	n = 2,043	n = 2,043
□ Dutasteride	n = 702	n = 630	n = 2,020	n = 2,027	n = 2,028

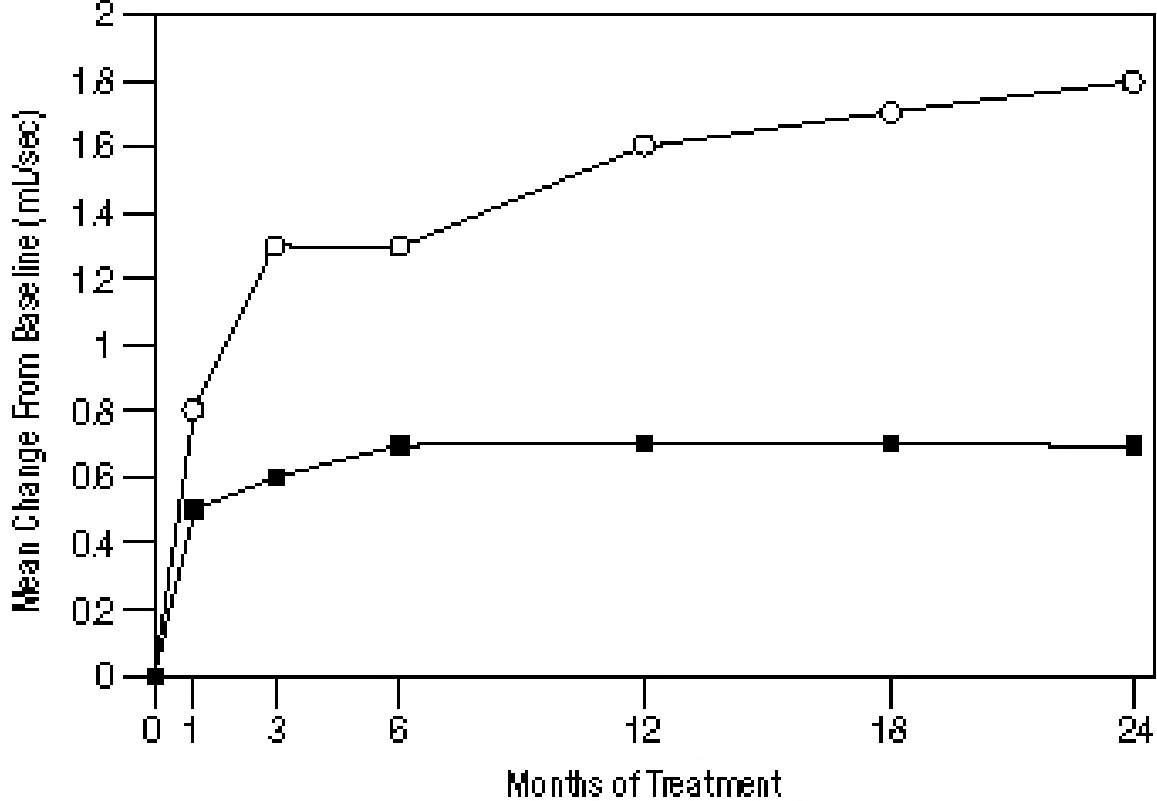
198
199

200 **Effect on Maximum Urine Flow Rate:** A mean peak urine flow rate (Q_{max}) of ≤ 15 mL/sec
201 was required for study entry. Q_{max} was approximately 10 mL/sec at baseline across the 3 pivotal
202 studies.

203 Differences between the 2 groups were statistically significant from baseline at Month 3 in all
204 3 studies and were maintained through Month 12. At Month 12, the mean increase in Q_{max} across
205 the 3 studies pooled was 1.6 mL/sec for dutasteride and 0.7 mL/sec for placebo; the mean
206 difference (dutasteride minus placebo) was 0.8 mL/sec (range, 0.7 to 1.0 mL/sec in each of the
207 3 studies, $p < 0.001$). At Month 24, the mean increase in Q_{max} was 1.8 mL/sec for dutasteride and
208 0.7 mL/sec for placebo, with a mean difference of 1.1 mL/sec (range, 1.0 to 1.2 mL/sec in each
209 of the 3 studies, $p < 0.001$). See Figure 5. The increase in maximum urine flow rate seen during
210 the first 2 years of double-blind treatment was maintained throughout an additional 2 years of
211 open-label extension studies.

212

213 **Figure 5. Q_{max} Change from Baseline (Pivotal Studies Pooled)**



■ Placebo n = 2,101 n = 2,105 n = 2,105 n = 2,105
 □ Dutasteride n = 2,103 n = 2,104 n = 2,104 n = 2,104

214
215

216 **Summary of Clinical Studies:** Data from 3 large, well-controlled efficacy studies
 217 demonstrate that treatment with AVODART (0.5 mg once daily) reduces the risk of both AUR
 218 and BPH-related surgical intervention relative to placebo, improves BPH-related symptoms,
 219 decreases prostate volume, and increases maximum urinary flow rates. These data suggest that
 220 AVODART arrests the disease process of BPH in men with an enlarged prostate.

221 **INDICATIONS AND USAGE**

222 AVODART is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH)
 223 in men with an enlarged prostate to:

- 224 • Improve symptoms
- 225 • Reduce the risk of acute urinary retention
- 226 • Reduce the risk of the need for BPH-related surgery

227 **CONTRAINDICATIONS**

228 AVODART is contraindicated for use in women and children.

229 AVODART is contraindicated for patients with known hypersensitivity (e.g., angioedema) to
 230 dutasteride, other 5 α -reductase inhibitors, or any component of the preparation.

231 **WARNINGS**

232 **Exposure of Women—Risk to Male Fetus:** Dutasteride is absorbed through the skin.
233 Therefore, women who are pregnant or may be pregnant should not handle AVODART Soft
234 Gelatin Capsules because of the possibility of absorption of dutasteride and the potential risk of a
235 fetal anomaly to a male fetus (see CONTRAINDICATIONS). In addition, women should use
236 caution whenever handling AVODART Soft Gelatin Capsules. If contact is made with leaking
237 capsules, the contact area should be washed immediately with soap and water.

238 **PRECAUTIONS**

239 **General:** Lower urinary tract symptoms of BPH can be indicative of other urological diseases,
240 including prostate cancer. Patients should be assessed to rule out other urological diseases prior
241 to treatment with AVODART. Patients with a large residual urinary volume and/or severely
242 diminished urinary flow may not be good candidates for 5 α -reductase inhibitor therapy and
243 should be carefully monitored for obstructive uropathy.

244 **Blood Donation:** Men being treated with dutasteride should not donate blood until at least
245 6 months have passed following their last dose. The purpose of this deferred period is to prevent
246 administration of dutasteride to a pregnant female transfusion recipient.

247 **Use in Hepatic Impairment:** The effect of hepatic impairment on dutasteride
248 pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a
249 half-life of approximately 5 weeks at steady state, caution should be used in the administration of
250 dutasteride to patients with liver disease.

251 **Use with Potent CYP3A4 Inhibitors:** Although dutasteride is extensively metabolized, no
252 metabolically based drug interaction studies have been conducted. The effect of potent CYP3A4
253 inhibitors has not been studied. Because of the potential for drug-drug interactions, care should
254 be taken when administering dutasteride to patients taking potent, chronic CYP3A4 enzyme
255 inhibitors (e.g., ritonavir).

256 **Effects on Prostate-Specific Antigen and Prostate Cancer Detection:** Digital rectal
257 examinations, as well as other evaluations for prostate cancer, should be performed on patients
258 with BPH prior to initiating therapy with AVODART and periodically thereafter.

259 Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months
260 of treatment and approximately 50% following 6, 12, and 24 months of treatment. This decrease
261 is predictable over the entire range of PSA values, although it may vary in individual patients.
262 Therefore, for interpretation of serial PSAs in a man taking AVODART, a new baseline PSA
263 concentration should be established after 3 to 6 months of treatment, and this new value should
264 be used to assess potentially cancer-related changes in PSA. To interpret an isolated PSA value
265 in a man treated with AVODART for 6 months or more, the PSA value should be doubled for
266 comparison with normal values in untreated men.

267 The free-to-total PSA ratio (percent free PSA) remains constant at Month 12, even under the
268 influence of AVODART. If clinicians elect to use percent free PSA as an aid in the detection of
269 prostate cancer in men receiving AVODART, no adjustment to its value appears necessary.

270 **Information for Patients:** Physicians should instruct their patients to read the Patient
271 Information leaflet before starting therapy with AVODART and to reread it upon prescription
272 renewal for new information regarding the use of AVODART.

273 AVODART Soft Gelatin Capsules should not be handled by a woman who is pregnant or who
274 may become pregnant because of the potential for absorption of dutasteride and the subsequent
275 potential risk to a developing male fetus (see CONTRAINDICATIONS and WARNINGS:
276 Exposure of Women—Risk to Male Fetus).

277 Physicians should inform patients that ejaculate volume might be decreased in some patients
278 during treatment with AVODART. This decrease does not appear to interfere with normal sexual
279 function. In clinical trials, impotence and decreased libido, considered by the investigator to be
280 drug-related, occurred in a small number of patients treated with AVODART or placebo (see
281 ADVERSE REACTIONS: Table 1).

282 Men treated with dutasteride should not donate blood until at least 6 months have passed
283 following their last dose to prevent pregnant women from receiving dutasteride through blood
284 transfusion (see PRECAUTIONS: Blood Donation).

285 **Drug Interactions:** Care should be taken when administering dutasteride to patients taking
286 potent, chronic CYP3A4 inhibitors (see PRECAUTIONS: Use with Potent CYP3A4 Inhibitors).

287 Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human
288 cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a
289 concentration of 1,000 ng/mL, 25 times greater than steady-state serum concentrations in
290 humans. In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam, or
291 phenytoin from plasma protein binding sites, nor do these model compounds displace
292 dutasteride.

293 **Digoxin:** In a study of 20 healthy volunteers, AVODART did not alter the steady-state
294 pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for
295 3 weeks.

296 **Warfarin:** In a study of 23 healthy volunteers, 3 weeks of treatment with AVODART
297 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or
298 alter the effect of warfarin on prothrombin time when administered with warfarin.

299 **Alpha-Adrenergic Blocking Agents:** In a single sequence, crossover study in healthy
300 volunteers, the administration of tamsulosin or terazosin in combination with AVODART had no
301 effect on the steady-state pharmacokinetics of either alpha-adrenergic blocker. The percent
302 change in DHT concentrations was similar for AVODART alone compared with the combination
303 treatment.

304 A clinical trial was conducted in which dutasteride and tamsulosin were administered
305 concomitantly for 24 weeks followed by 12 weeks of treatment with either the dutasteride and
306 tamsulosin combination or dutasteride monotherapy. Results from the second phase of the trial
307 revealed no excess of serious adverse events or discontinuations due to adverse events in the
308 combination group compared to the dutasteride monotherapy group.

309 **Calcium Channel Antagonists:** In a population pharmacokinetics analysis, a decrease in
310 clearance of dutasteride was noted when co-administered with the CYP3A4 inhibitors verapamil
311 (-37%, n = 6) and diltiazem (-44%, n = 5). In contrast, no decrease in clearance was seen when
312 amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was
313 co-administered with dutasteride (+7%, n = 4).

314 The decrease in clearance and subsequent increase in exposure to dutasteride in the presence
315 of verapamil and diltiazem is not considered to be clinically significant. No dose adjustment is
316 recommended.

317 **Cholestyramine:** Administration of a single 5-mg dose of AVODART followed 1 hour
318 later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal
319 volunteers.

320 **Other Concomitant Therapy:** Although specific interaction studies were not performed
321 with other compounds, approximately 90% of the subjects in the 3 Phase III pivotal efficacy
322 studies receiving AVODART were taking other medications concomitantly. No clinically
323 significant adverse interactions could be attributed to the combination of AVODART and
324 concurrent therapy when AVODART was co-administered with anti-hyperlipidemics,
325 angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium
326 channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs),
327 phosphodiesterase Type V inhibitors, and quinolone antibiotics.

328 **Drug/Laboratory Test Interactions: Effects on Prostate-Specific Antigen:** PSA levels
329 generally decrease in patients treated with AVODART as the prostate volume decreases. In
330 approximately one-half of the subjects, a 20% decrease in PSA is seen within the first month of
331 therapy. After 6 months of therapy, PSA levels stabilize to a new baseline that is approximately
332 50% of the pre-treatment value. Results of subjects treated with AVODART for up to 2 years
333 indicate this 50% reduction in PSA is maintained. Therefore, a new baseline PSA concentration
334 should be established after 3 to 6 months of treatment with AVODART (see PRECAUTIONS:
335 Effects on PSA and Prostate Cancer Detection).

336 **Hormone Levels:** In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day
337 (n = 26) resulted in no clinically significant change compared with placebo (n = 23) in sex
338 hormone binding globulin, estradiol, luteinizing hormone, follicle-stimulating hormone,
339 thyroxine (free T4), and dehydroepiandrosterone. Statistically significant, baseline-adjusted
340 mean increases compared with placebo were observed for total testosterone at 8 weeks
341 (97.1 ng/dL, p<0.003) and thyroid-stimulating hormone (TSH) at 52 weeks (0.4 mIU/mL,
342 p<0.05). The median percentage changes from baseline within the dutasteride group were 17.9%
343 for testosterone at 8 weeks and 12.4% for TSH at 52 weeks. After stopping dutasteride for
344 24 weeks, the mean levels of testosterone and TSH had returned to baseline in the group of
345 subjects with available data at the visit. In patients with BPH treated with dutasteride 0.5 mg/day
346 for 4 years, the median decrease in serum DHT was 94% at 1 year, 93% at 2 years, and 95% at
347 both 3 and 4 years. The median increase in serum testosterone was 19% at both 1 and 2 years,
348 26% at 3 years, and 22% at 4 years, but the mean and median levels remained within the

349 physiologic range. In patients with BPH treated with dutasteride in a large Phase III trial, there
350 was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at both 12
351 and 24 months.

352 **Reproductive Function:** The effects of dutasteride 0.5 mg/day on semen characteristics
353 were evaluated in normal volunteers aged 18 to 52 (n = 27 dutasteride, n = 23 placebo)
354 throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the
355 mean percent reduction from baseline in total sperm count, semen volume, and sperm motility
356 were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from
357 baseline in the placebo group. Sperm concentration and sperm morphology were unaffected.
358 After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride
359 group remained 23% lower than baseline. While mean values for all semen parameters at all time
360 points remained within the normal ranges and did not meet predefined criteria for a clinically
361 significant change (30%), two subjects in the dutasteride group had decreases in sperm count of
362 greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The
363 clinical significance of dutasteride's effect on semen characteristics for an individual patient's
364 fertility is not known.

365 **Central Nervous System Toxicity:** In rats and dogs, repeated oral administration of
366 dutasteride resulted in some animals showing signs of non-specific, reversible,
367 centrally-mediated toxicity without associated histopathological changes at exposure 425- and
368 315-fold the expected clinical exposure (of parent drug), respectively.

369 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** A 2-year
370 carcinogenicity study was conducted in B6C3F1 mice at doses of 3, 35, 250, and 500 mg/kg/day
371 for males and 3, 35, and 250 mg/kg/day for females; an increased incidence of benign
372 hepatocellular adenomas was noted at 250 mg/kg/day (290-fold the expected clinical exposure to
373 a 0.5 mg daily dose) in females only. Two of the 3 major human metabolites have been detected
374 in mice. The exposure to these metabolites in mice is either lower than in humans or is not
375 known.

376 In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and 53 mg/kg/day
377 for males and 0.8, 6.3, and 15 mg/kg/day for females, there was an increase in Leydig cell
378 adenomas in the testes at 53 mg/kg/day (135-fold the expected clinical exposure). An increased
379 incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/day (52-fold the expected clinical
380 exposure) and 53 mg/kg/day in male rats. A positive correlation between proliferative changes in
381 the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated
382 with 5 α -reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-
383 testicular axis following 5 α -reductase inhibition. At tumorigenic doses in rats, luteinizing
384 hormone levels in rats were increased by 167%. In this study, the major human metabolites were
385 tested for carcinogenicity at approximately 1 to 3 times the expected clinical exposure.

386 **Mutagenesis:** Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay
387 (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The

388 results did not indicate any genotoxic potential of the parent drug. Two major human metabolites
389 were also negative in either the Ames test or an abbreviated Ames test.

390 **Impairment of Fertility:** Treatment of sexually mature male rats with dutasteride at doses
391 of 0.05, 10, 50, and 500 mg/kg/day (0.1- to 110-fold the expected clinical exposure of parent
392 drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility; reduced
393 cauda epididymal (absolute) sperm counts but not sperm concentration (at 50 and
394 500 mg/kg/day); reduced weights of the epididymis, prostate, and seminal vesicles; and
395 microscopic changes in the male reproductive organs. The fertility effects were reversed by
396 recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery
397 period. The 5 α -reductase-related changes consisted of cytoplasmic vacuolation of tubular
398 epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with
399 decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were
400 no longer present at recovery week 14 in the low-dose group and were partly recovered in the
401 remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/mL) were detected in the
402 serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/ day for 29 to
403 30 weeks.

404 In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5,
405 and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption and feminization of
406 male fetuses (decreased anogenital distance) at doses of ≥ 2.5 mg/kg/day (2- to 10-fold the
407 clinical exposure of parent drug in men). Fetal body weights were also reduced at
408 ≥ 0.05 mg/kg/day in rats (< 0.02 -fold the human exposure).

409 **Pregnancy:** Pregnancy Category **X** (see CONTRAINDICATIONS). AVODART is
410 contraindicated for use in women. AVODART has not been studied in women because
411 preclinical data suggest that the suppression of circulating levels of dihydrotestosterone may
412 inhibit the development of the external genital organs in a male fetus carried by a woman
413 exposed to dutasteride.

414 In an intravenous embryo-fetal development study in the rhesus monkey (12/group),
415 administration of dutasteride at 400, 780, 1,325, or 2,010 ng/day on gestation days 20 to 100
416 did not adversely affect development of male external genitalia. Reduction of fetal adrenal
417 weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights
418 were observed in monkeys treated with the highest dose. Based on the highest measured
419 semen concentration of dutasteride in treated men (14 ng/mL), these doses represent 0.8 to
420 16 times based on blood levels of parent drug (32 to 186 times based on a ng/kg daily dose)
421 the potential maximum exposure of a 50-kg human female to 5 mL semen daily from a
422 dutasteride-treated man, assuming 100% absorption. Dutasteride is highly bound to proteins in
423 human semen ($> 96\%$), potentially reducing the amount of dutasteride available for vaginal
424 absorption.

425 In an embryo-fetal development study in female rats, oral administration of dutasteride at
426 doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in feminization of male fetuses (decreased
427 anogenital distance) and male offspring (nipple development, hypospadias, and distended

428 preputial glands) at all doses (0.07- to 111-fold the expected male clinical exposure). An
429 increase in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was
430 observed at doses ≥ 2.5 mg/kg/day (15- to 111-fold the expected clinical exposure). Increased
431 incidences of skeletal variations considered to be delays in ossification associated with
432 reduced body weight were observed at doses of 12.5 and 30 mg/kg/day (56- to 111-fold the
433 expected clinical exposure).

434 In an oral pre- and post-natal development study in rats, dutasteride doses of 0.05, 2.5, 12.5,
435 or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia (i.e.,
436 decreased anogenital distance, increased incidence of hypospadias, nipple development) of F1
437 generation male offspring occurred at doses ≥ 2.5 mg/kg/day (14- to 90-fold the expected clinical
438 exposure in men). At a daily dose of 0.05 mg/kg/day (0.05-fold the expected clinical exposure),
439 evidence of feminization was limited to a small, but statistically significant, decrease in
440 anogenital distance. Doses of 2.5 to 30 mg/kg/day resulted in prolonged gestation in the parental
441 females and a decrease in time to vaginal patency for female offspring and decrease prostate and
442 seminal vesicle weights in male offspring. Effects on newborn startle response were noted at
443 doses greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day.

444 Feminization of male fetuses is an expected physiological consequence of inhibition of the
445 conversion of testosterone to DHT by 5α -reductase inhibitors. These results are similar to
446 observations in male infants with genetic 5α -reductase deficiency.

447 In the rabbit, embryo-fetal study doses of 30, 100, and 200 mg/kg (28- to 93-fold the expected
448 clinical exposure in men) were administered orally on days 7 to 29 of pregnancy to encompass
449 the late period of external genitalia development. Histological evaluation of the genital papilla of
450 fetuses revealed evidence of feminization of the male fetus at all doses. A second embryo-fetal
451 study in rabbits at doses of 0.05, 0.4, 3.0, and 30 mg/kg/day (0.3- to 53-fold the expected clinical
452 exposure) also produced evidence of feminization of the genitalia in male fetuses at all doses. It
453 is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

454 **Nursing Mothers:** AVODART is not indicated for use in women. It is not known whether
455 dutasteride is excreted in human breast milk.

456 **Pediatric Use:** AVODART is not indicated for use in the pediatric population. Safety and
457 effectiveness in the pediatric population have not been established.

458 **Geriatric Use:** Of 2,167 male subjects treated with AVODART in 3 clinical studies, 60% were
459 65 and over and 15% were 75 and over. No overall differences in safety or efficacy were
460 observed between these subjects and younger subjects. Other reported clinical experience has not
461 identified differences in responses between the elderly and younger patients.

462 **ADVERSE REACTIONS**

463 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
464 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of
465 another drug and may not reflect the rates observed in practice. The adverse reaction information

466 from clinical trials does, however, provide a basis for identifying the adverse events that appear
467 to be related to drug use and for approximating rates.

468 Most adverse reactions were mild or moderate and generally resolved while on treatment in
469 both the AVODART and placebo groups. The most common adverse events leading to
470 withdrawal in both treatment groups were associated with the reproductive system.

471 Over 4,300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg
472 daily doses of AVODART in 3 identical 2-year, placebo-controlled, double-blind, Phase 3
473 treatment studies, each with 2-year open-label extensions. During the double-blind treatment
474 period, 2,167 male subjects were exposed to AVODART, including 1,772 exposed for 1 year and
475 1,510 exposed for 2 years. When including the open-label extensions, 1,009 male subjects were
476 exposed to AVODART for 3 years and 812 were exposed for 4 years. The population was aged
477 47 to 94 years (mean age, 66 years) and greater than 90% Caucasian. Over the 2-year
478 double-blind treatment period, 376 subjects (9% of each treatment group) were withdrawn from
479 the studies due to adverse experiences, most commonly associated with the reproductive system,
480 with similar findings during the 2-year open-label extensions. Withdrawals due to adverse events
481 considered by the investigator to have a reasonable possibility of being caused by the study
482 medication occurred in 4% of the subjects receiving AVODART and in 3% of the subjects
483 receiving placebo. Table 1 summarizes clinical adverse reactions that were reported by the
484 investigator as drug-related in at least 1% of subjects receiving AVODART and at a higher
485 incidence than subjects receiving placebo.

486

487 **Table 1. Drug-Related Adverse Events* Reported in ≥1% Subjects Over a 24-Month**
 488 **Period and More Frequently in the Dutasteride Group Than the Placebo Group**
 489 **(Pivotal Studies Pooled)**

Adverse Events Dutasteride (n) Placebo (n)	Adverse Event Onset			
	Month 0-6 (n = 2,167) (n = 2,158)	Month 7-12 (n = 1,901) (n = 1,922)	Month 13-18 (n = 1,725) (n = 1,714)	Month 19-24 (n = 1,605) (n = 1,555)
Impotence				
Dutasteride	4.7%	1.4%	1.0%	0.8%
Placebo	1.7%	1.5%	0.5%	0.9%
Decreased libido				
Dutasteride	3.0%	0.7%	0.3%	0.3%
Placebo	1.4%	0.6%	0.2%	0.1%
Ejaculation disorder				
Dutasteride	1.4%	0.5%	0.5%	0.1%
Placebo	0.5%	0.3%	0.1%	0.0%
Gynecomastia [†]				
Dutasteride	0.5%	0.8%	1.1%	0.6%
Placebo	0.2%	0.3%	0.3%	0.1%

490 * **A drug-related adverse event is one considered by the investigator to have a**
 491 **reasonable possibility of being caused by the study medication. In assessing causality,**
 492 **investigators were asked to select from 1 of 2 options: reasonably related to study**
 493 **medication or unrelated to study medication.**

494 [†] Includes breast tenderness and breast enlargement.

495
 496 **Long-Term Treatment (Up to 4 Years):** There is no evidence of increased drug-related
 497 sexual adverse events (impotence, decreased libido and ejaculation disorder) or gynecomastia
 498 with increased duration of treatment. The relationship between long-term use of dutasteride and
 499 male breast neoplasia is currently unknown.

500 **Postmarketing Experience:** The following adverse reactions have been identified during
 501 postapproval use of AVODART. Because these reactions are reported voluntarily from a
 502 population of uncertain size, it is not always possible to reliably estimate their frequency or
 503 establish a causal relationship to drug exposure. Decisions to include these reactions in labeling
 504 are based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency
 505 of reporting, or (3) potential causal connection to AVODART.

506 **Immune System Disorders:** Allergic reactions, including rash, pruritus, urticaria,
 507 localized edema, serious skin reactions, angioedema.

508 **OVERDOSAGE**

509 In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose)
510 for 7 days have been administered without significant safety concerns. In a clinical study, daily
511 doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for 6 months with
512 no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

513 There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage
514 symptomatic and supportive treatment should be given as appropriate, taking the long half-life of
515 dutasteride into consideration.

516 **DOSAGE AND ADMINISTRATION**

517 The recommended dose of AVODART is 1 capsule (0.5 mg) taken orally once a day. The
518 capsules should be swallowed whole and not chewed or opened, as contact with the capsule
519 contents may result in irritation of the oropharyngeal mucosa. AVODART may be administered
520 with or without food.

521 No dosage adjustment is necessary for subjects with renal impairment or for the elderly (see
522 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special Populations: Geriatric and Renal*
523 *Impairment*). Due to the absence of data in patients with hepatic impairment, no dosage
524 recommendation can be made (see PRECAUTIONS: General).

525 **HOW SUPPLIED**

526 AVODART Soft Gelatin Capsules 0.5 mg are oblong, opaque, dull yellow, gelatin capsules
527 imprinted with “GX CE2” in red ink on one side packaged in bottles of 30 (NDC 0173-0712-15)
528 and 90 (NDC 0173-0712-04) with child-resistant closures.

529 **Storage and Handling:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see
530 USP Controlled Room Temperature].

531 Dutasteride is absorbed through the skin. AVODART Soft Gelatin capsules should not be
532 handled by women who are pregnant or who may become pregnant because of the potential for
533 absorption of dutasteride and the subsequent potential risk to a developing male fetus (see
534 CLINICAL PHARMACOLOGY: Pharmacokinetics, WARNINGS: Exposure of Women—Risk
535 to Male Fetus, and PRECAUTIONS: Information for Patients and Pregnancy).

536
537



538
539 Manufactured by Catalent Pharma Solutions
540 Beinheim, France for
541 GlaxoSmithKline
542 Research Triangle Park, NC 27709

543
544 ©2008, GlaxoSmithKline. All rights reserved.

545

546 February 2008

AVT:2PI