

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVODART safely and effectively. See full prescribing information for AVODART.

AVODART (dutasteride) Soft Gelatin Capsules
Initial U.S. Approval: 2001

RECENT MAJOR CHANGES

Indications and Usage, Limitations of Use (1.3) June 2011
Warnings and Precautions, Increased Risk of High-grade Prostate Cancer (5.2) June 2011
Warnings and Precautions, Effects on Prostate-Specific Antigen (PSA) and the Use of PSA in Prostate Cancer Detection (5.1) June 2010

INDICATIONS AND USAGE

AVODART is a 5 alpha-reductase inhibitor indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to: (1.1)

- improve symptoms,
- reduce the risk of acute urinary retention, and
- reduce the risk of the need for BPH-related surgery.

AVODART in combination with the alpha adrenergic antagonist, tamsulosin, is indicated for the treatment of symptomatic BPH in men with an enlarged prostate. (1.2)

Limitations of Use: AVODART is not approved for the prevention of prostate cancer. (1.3)

DOSAGE AND ADMINISTRATION

Monotherapy: 0.5 mg once daily. (2.1)
Combination with tamsulosin: 0.5 mg once daily and tamsulosin 0.4 mg once daily. (2.2)
Dosing considerations: Swallow whole. May take with or without food. (2)

DOSAGE FORMS AND STRENGTHS

0.5-mg soft gelatin capsules (3)

CONTRAINDICATIONS

- Pregnancy and women of childbearing potential. (4, 5.4, 8.1)
- Pediatric patients. (4)
- Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to AVODART or other 5 alpha-reductase inhibitors. (4)

WARNINGS AND PRECAUTIONS

- AVODART reduces serum prostate-specific antigen (PSA) concentration by approximately 50%. However, any confirmed increase in PSA while on AVODART may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for untreated men. (5.1)
- AVODART may increase the risk of high-grade prostate cancer. (5.2, 6.1)
- Assess patients to rule out other urological diseases, including prostate cancer, prior to prescribing AVODART. (5.3)
- Women who are pregnant or could become pregnant should not handle AVODART Capsules due to potential risk to a male fetus. (5.4, 8.1)
- Patients should not donate blood until 6 months after their last dose of AVODART. (5.5)

ADVERSE REACTIONS

The most common adverse reactions, reported in $\geq 1\%$ of patients treated with AVODART and more commonly than in patients treated with placebo, are impotence, decreased libido, ejaculation disorders, and breast disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Use with caution in patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir). (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: June 2011

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 Monotherapy**

4 AVODART® (dutasteride) Soft Gelatin Capsules are indicated for the treatment of
5 symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

- 6 • improve symptoms,
- 7 • reduce the risk of acute urinary retention (AUR), and
- 8 • reduce the risk of the need for BPH-related surgery.

9 **1.2 Combination With Alpha Adrenergic Antagonist**

10 AVODART in combination with the alpha adrenergic antagonist, tamsulosin, is indicated
11 for the treatment of symptomatic BPH in men with an enlarged prostate.

12 **1.3 Limitations of Use**

13 AVODART is not approved for the prevention of prostate cancer.

14 **2 DOSAGE AND ADMINISTRATION**

15 The capsules should be swallowed whole and not chewed or opened, as contact with the
16 capsule contents may result in irritation of the oropharyngeal mucosa. AVODART may be
17 administered with or without food.

18 **2.1 Monotherapy**

19 The recommended dose of AVODART is 1 capsule (0.5 mg) taken once daily.

20 **2.2 Combination With Alpha Adrenergic Antagonist**

21 The recommended dose of AVODART is 1 capsule (0.5 mg) taken once daily and
22 tamsulosin 0.4 mg taken once daily.

23 **3 DOSAGE FORMS AND STRENGTHS**

24 0.5-mg, opaque, dull yellow, gelatin capsules imprinted with “GX CE2” in red ink on one
25 side.

26 **4 CONTRAINDICATIONS**

27 AVODART is contraindicated for use in:

- 28 • Pregnancy. In animal reproduction and developmental toxicity studies, dutasteride inhibited
29 development of male fetus external genitalia. Therefore, AVODART may cause fetal harm
30 when administered to a pregnant woman. If AVODART is used during pregnancy or if the
31 patient becomes pregnant while taking AVODART, the patient should be apprised of the
32 potential hazard to the fetus [*see Warnings and Precautions (5.4), Use in Specific*
33 *Populations (8.1)*].
- 34 • Women of childbearing potential [*see Warnings and Precautions (5.4), Use in Specific*
35 *Populations (8.1)*].
- 36 • Pediatric patients [*see Use in Specific Populations (8.4)*].

- 37 • Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious
38 skin reactions, angioedema) to AVODART or other 5 alpha-reductase inhibitors [*see Adverse*
39 *Reactions (6.2)*].

40 **5 WARNINGS AND PRECAUTIONS**

41 **5.1 Effects on Prostate-Specific Antigen (PSA) and the Use of PSA in Prostate** 42 **Cancer Detection**

43 In clinical studies, AVODART reduced serum PSA concentration by approximately 50%
44 within 3 to 6 months of treatment. This decrease was predictable over the entire range of PSA
45 values in patients with symptomatic BPH, although it may vary in individuals. AVODART may
46 also cause decreases in serum PSA in the presence of prostate cancer. To interpret serial PSAs in
47 men taking AVODART, a new PSA baseline should be established at least 3 months after
48 starting treatment and PSA monitored periodically thereafter. Any confirmed increase from the
49 lowest PSA value while on AVODART may signal the presence of prostate cancer and should be
50 evaluated, even if PSA levels are still within the normal range for men not taking a 5 alpha-
51 reductase inhibitor. Noncompliance with AVODART may also affect PSA test results.

52 To interpret an isolated PSA value in a man treated with AVODART for 3 months or
53 more, the PSA value should be doubled for comparison with normal values in untreated men.

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

57 Coadministration of dutasteride and tamsulosin resulted in similar changes to serum PSA
58 as dutasteride monotherapy.

59 **5.2 Increased Risk of High-grade Prostate Cancer**

60 In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline
61 PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by
62 Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of
63 Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus
64 placebo 0.5%) [*see Indications and Usage (1.3), Adverse Reactions (6.1)*]. In a 7-year
65 placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg,
66 PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride
67 1.8% versus placebo 1.1%).

68 5 alpha-reductase inhibitors may increase the risk of development of high-grade prostate
69 cancer. Whether the effect of 5 alpha-reductase inhibitors to reduce prostate volume, or study-
70 related factors, impacted the results of these studies has not been established.

71 **5.3 Evaluation for Other Urological Diseases**

72 Lower urinary tract symptoms of BPH can be indicative of other urological diseases,
73 including prostate cancer. Patients should be assessed to rule out prostate cancer and other
74 urological diseases prior to treatment with AVODART and periodically thereafter.

75 **5.4 Exposure of Women—Risk to Male Fetus**

76 AVODART Capsules should not be handled by a woman who is pregnant or who could
77 become pregnant. Dutasteride is absorbed through the skin and could result in unintended fetal
78 exposure. If a woman who is pregnant or who could become pregnant comes in contact with
79 leaking dutasteride capsules, the contact area should be washed immediately with soap and water
80 [see Use in Specific Populations (8.1)].

81 **5.5 Blood Donation**

82 Men being treated with AVODART should not donate blood until at least 6 months have
83 passed following their last dose. The purpose of this deferred period is to prevent administration
84 of dutasteride to a pregnant female transfusion recipient.

85 **5.6 Effect on Semen Characteristics**

86 The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal
87 volunteers aged 18 to 52 (n = 27 dutasteride, n = 23 placebo) throughout 52 weeks of treatment
88 and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reductions from
89 baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%,
90 respectively, in the dutasteride group when adjusted for changes from baseline in the placebo
91 group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of
92 follow-up, the mean percent change in total sperm count in the dutasteride group remained 23%
93 lower than baseline. While mean values for all semen parameters at all time-points remained
94 within the normal ranges and did not meet predefined criteria for a clinically significant change
95 (30%), 2 subjects in the dutasteride group had decreases in sperm count of greater than 90%
96 from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical
97 significance of dutasteride's effect on semen characteristics for an individual patient's fertility is
98 not known.

99 **6 ADVERSE REACTIONS**

100 **6.1 Clinical Trials Experience**

101 Because clinical trials are conducted under widely varying conditions, adverse reaction
102 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
103 clinical trial of another drug and may not reflect the rates observed in practice.

104 From clinical trials with AVODART as monotherapy or in combination with tamsulosin:

- 105 • The most common adverse reactions reported in subjects receiving AVODART were
106 impotence, decreased libido, breast disorders (including breast enlargement and tenderness),
107 and ejaculation disorders. The most common adverse reactions reported in subjects receiving
108 combination therapy (AVODART plus tamsulosin) were impotence, decreased libido, breast
109 disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness.
110 Ejaculation disorders occurred significantly more in subjects receiving combination therapy
111 (11%) compared with those receiving AVODART (2%) or tamsulosin (4%) as monotherapy.
- 112 • Study withdrawal due to adverse reactions occurred in 4% of subjects receiving AVODART,
113 and 3% of subjects receiving placebo in placebo-controlled trials with AVODART. The most
114 common adverse reaction leading to study withdrawal was impotence (1%).

- In the clinical trial evaluating the combination therapy, study withdrawal due to adverse reactions occurred in 6% of subjects receiving combination therapy (AVODART plus tamsulosin) and 4% of subjects receiving AVODART or tamsulosin as monotherapy. The most common adverse reaction in all treatment arms leading to study withdrawal was erectile dysfunction (1% to 1.5%).

Monotherapy: Over 4,300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg daily doses of AVODART in three identical 2-year, placebo-controlled, double-blind, Phase 3 treatment studies, each followed by a 2-year open-label extension. During the double-blind treatment period, 2,167 male subjects were exposed to AVODART, including 1,772 exposed for 1 year and 1,510 exposed for 2 years. When including the open-label extensions, 1,009 male subjects were exposed to AVODART for 3 years and 812 were exposed for 4 years. The population was aged 47 to 94 years (mean age: 66 years) and greater than 90% were Caucasian. Table 1 summarizes clinical adverse reactions reported in at least 1% of subjects receiving AVODART and at a higher incidence than subjects receiving placebo.

Table 1. Adverse Reactions Reported in ≥1% of Subjects Over a 24-Month Period and More Frequently in the Group Receiving AVODART Than the Placebo Group (Randomized, Double-Blind, Placebo-Controlled Studies Pooled) by Time of Onset

Adverse Reaction	Adverse Reaction Time of Onset			
	Months 0-6 (n = 2,167)	Months 7-12 (n = 1,901)	Months 13-18 (n = 1,725)	Months 19-24 (n = 1,605)
AVODART (n)				
Placebo (n)	(n = 2,158)	(n = 1,922)	(n = 1,714)	(n = 1,555)
Impotence				
AVODART	4.7%	1.4%	1.0%	0.8%
Placebo	1.7%	1.5%	0.5%	0.9%
Decreased libido				
AVODART	3.0%	0.7%	0.3%	0.3%
Placebo	1.4%	0.6%	0.2%	0.1%
Ejaculation disorders				
AVODART	1.4%	0.5%	0.5%	0.1%
Placebo	0.5%	0.3%	0.1%	0.0%
Breast disorders ^a				
AVODART	0.5%	0.8%	1.1%	0.6%
Placebo	0.2%	0.3%	0.3%	0.1%

^a Includes breast tenderness and breast enlargement.

Long-Term Treatment (Up to 4 Years):

High-grade Prostate Cancer: The REDUCE trial was a randomized, double-blind,

137 placebo-controlled trial that enrolled 8,231 men aged 50 to 75 years with a serum PSA of
138 2.5 ng/mL to 10 ng/mL and a negative prostate biopsy within the previous 6 months. Subjects
139 were randomized to receive placebo (N = 4,126) or 0.5-mg daily doses of AVODART
140 (N = 4,105) for up to 4 years. The mean age was 63 years and 91% were Caucasian. Subjects
141 underwent protocol-mandated scheduled prostate biopsies at 2 and 4 years of treatment or had
142 “for-cause biopsies” at non-scheduled times if clinically indicated. There was a higher incidence
143 of Gleason score 8-10 prostate cancer in men receiving AVODART (1.0%) compared with men
144 on placebo (0.5%) [see *Indications and Usage (1.3), Warnings and Precautions (5.2)*]. In a
145 7-year placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg,
146 PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride
147 1.8% versus placebo 1.1%).

148 No clinical benefit has been demonstrated in patients with prostate cancer treated with
149 AVODART.

150 Reproductive and Breast Disorders: In the 3 pivotal placebo-controlled BPH trials
151 with AVODART, each 4 years in duration, there was no evidence of increased sexual adverse
152 reactions (impotence, decreased libido, and ejaculation disorder) or breast disorders with
153 increased duration of treatment. Among these 3 trials, there was 1 case of breast cancer in the
154 dutasteride group and 1 case in the placebo group. No cases of breast cancer were reported in any
155 treatment group in the 4-year CombAT trial or the 4-year REDUCE trial.

156 The relationship between long-term use of dutasteride and male breast neoplasia is
157 currently unknown.

158 Combination With Alpha-Blocker Therapy (CombAT): Over 4,800 male subjects with
159 BPH were randomly assigned to receive 0.5-mg AVODART, 0.4-mg tamsulosin, or combination
160 therapy (0.5-mg AVODART plus 0.4-mg tamsulosin) administered once daily in a 4-year
161 double-blind study. Overall, 1,623 subjects received monotherapy with AVODART;
162 1,611 subjects received monotherapy with tamsulosin; and 1,610 subjects received combination
163 therapy. The population was aged 49 to 88 years (mean age: 66 years) and 88% were Caucasian.
164 Table 2 summarizes adverse reactions reported in at least 1% of subjects in the combination
165 group and at a higher incidence than subjects receiving monotherapy with AVODART or
166 tamsulosin.

167

168 **Table 2. Adverse Reactions Reported Over a 48-Month Period in ≥1% of Subjects and**
 169 **More Frequently in the Coadministration Therapy Group than the Groups Receiving**
 170 **Monotherapy With AVODART or Tamsulosin (CombAT) by Time of Onset**

Adverse Reaction	Adverse Reaction Time of Onset				
	Year 1		Year 2	Year 3	Year 4
	Months 0-6	Months 7-12			
Combination ^a	(n = 1,610)	(n = 1,527)	(n = 1,428)	(n = 1,283)	(n = 1,200)
AVODART	(n = 1,623)	(n = 1,548)	(n = 1,464)	(n = 1,325)	(n = 1,200)
Tamsulosin	(n = 1,611)	(n = 1,545)	(n = 1,468)	(n = 1,281)	(n = 1,112)
Ejaculation disorders ^b					
Combination	7.8%	1.6%	1.0%	0.5%	<0.1%
AVODART	1.0%	0.5%	0.5%	0.2%	0.3%
Tamsulosin	2.2%	0.5%	0.5%	0.2%	0.3%
Impotence ^c					
Combination	5.4%	1.1%	1.8%	0.9%	0.4%
AVODART	4.0%	1.1%	1.6%	0.6%	0.3%
Tamsulosin	2.6%	0.8%	1.0%	0.6%	1.1%
Decreased libido ^d					
Combination	4.5%	0.9%	0.8%	0.2%	0.0%
AVODART	3.1%	0.7%	1.0%	0.2%	0.0%
Tamsulosin	2.0%	0.6%	0.7%	0.2%	<0.1%
Breast disorders ^e					
Combination	1.1%	1.1%	0.8%	0.9%	0.6%
AVODART	0.9%	0.9%	1.2%	0.5%	0.7%
Tamsulosin	0.4%	0.4%	0.4%	0.2%	0.0%
Dizziness					
Combination	1.1%	0.4%	0.1%	<0.1%	0.2%
AVODART	0.5%	0.3%	0.1%	<0.1%	<0.1%
Tamsulosin	0.9%	0.5%	0.4%	<0.1%	0.0%

171 ^a Combination = AVODART 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

172 ^b Includes anorgasmia, retrograde ejaculation, semen volume decreased, orgasmic sensation
 173 decreased, orgasm abnormal, ejaculation delayed, ejaculation disorder, ejaculation failure, and
 174 premature ejaculation.

175 ^c Includes erectile dysfunction and disturbance in sexual arousal.

176 ^d Includes libido decreased, libido disorder, loss of libido, sexual dysfunction, and male sexual
 177 dysfunction.

178 ^e Includes breast enlargement, gynecomastia, breast swelling, breast pain, breast
179 tenderness, nipple pain, and nipple swelling.

180
181 **Cardiac Failure:** In CombAT, after 4 years of treatment, the incidence of the
182 composite term cardiac failure in the combination therapy group (12/1,610; 0.7%) was higher
183 than in either monotherapy group: AVODART, 2/1,623 (0.1%) and tamsulosin, 9/1,611 (0.6%).
184 Composite cardiac failure was also examined in a separate 4-year placebo-controlled trial
185 evaluating AVODART in men at risk for development of prostate cancer. The incidence of
186 cardiac failure in subjects taking AVODART was 0.6% (26/4,105) compared with 0.4%
187 (15/4,126) in subjects on placebo. A majority of subjects with cardiac failure in both studies had
188 co-morbidities associated with an increased risk of cardiac failure. Therefore, the clinical
189 significance of the numerical imbalances in cardiac failure is unknown. No causal relationship
190 between AVODART, alone or in combination with tamsulosin, and cardiac failure has been
191 established. No imbalance was observed in the incidence of overall cardiovascular adverse
192 events in either study.

193 **6.2 Postmarketing Experience**

194 The following adverse reactions have been identified during post-approval use of
195 AVODART. Because these reactions are reported voluntarily from a population of uncertain
196 size, it is not always possible to reliably estimate their frequency or establish a causal
197 relationship to drug exposure. These reactions have been chosen for inclusion due to a
198 combination of their seriousness, frequency of reporting, or potential causal connection to
199 AVODART.

200 Immune System Disorders: Hypersensitivity reactions, including rash, pruritus,
201 urticaria, localized edema, serious skin reactions, and angioedema.

202 Neoplasms: Male breast cancer.

203 **7 DRUG INTERACTIONS**

204 **7.1 Cytochrome P450 3A Inhibitors**

205 Dutasteride is extensively metabolized in humans by the CYP3A4 and CYP3A5
206 isoenzymes. The effect of potent CYP3A4 inhibitors on dutasteride has not been studied.
207 Because of the potential for drug-drug interactions, use caution when prescribing AVODART to
208 patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir) [*see Clinical*
209 *Pharmacology (12.3)*].

210 **7.2 Alpha Adrenergic Antagonists**

211 The administration of AVODART in combination with tamsulosin or terazosin has no
212 effect on the steady-state pharmacokinetics of either alpha-adrenergic antagonist. The effect of
213 administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters has not
214 been evaluated.

215 **7.3 Calcium Channel Antagonists**

216 Coadministration of verapamil or diltiazem decreases dutasteride clearance and leads to

217 increased exposure to dutasteride. The change in dutasteride exposure is not considered to be
218 clinically significant. No dose adjustment is recommended [see *Clinical Pharmacology (12.3)*].

219 **7.4 Cholestyramine**

220 Administration of a single 5-mg dose of AVODART followed 1 hour later by 12 g of
221 cholestyramine does not affect the relative bioavailability of dutasteride [see *Clinical*
222 *Pharmacology (12.3)*].

223 **7.5 Digoxin**

224 AVODART does not alter the steady-state pharmacokinetics of digoxin when
225 administered concomitantly at a dose of 0.5 mg/day for 3 weeks [see *Clinical Pharmacology*
226 *(12.3)*].

227 **7.6 Warfarin**

228 Concomitant administration of AVODART 0.5 mg/day for 3 weeks with warfarin does
229 not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of
230 warfarin on prothrombin time [see *Clinical Pharmacology (12.3)*].

231 **8 USE IN SPECIFIC POPULATIONS**

232 **8.1 Pregnancy**

233 Pregnancy Category X. AVODART is contraindicated for use in women of childbearing
234 potential and during pregnancy. AVODART is a 5 alpha-reductase inhibitor that prevents
235 conversion of testosterone to dihydrotestosterone (DHT), a hormone necessary for normal
236 development of male genitalia. In animal reproduction and developmental toxicity studies,
237 dutasteride inhibited normal development of external genitalia in male fetuses. Therefore,
238 AVODART may cause fetal harm when administered to a pregnant woman. If AVODART is
239 used during pregnancy or if the patient becomes pregnant while taking AVODART, the patient
240 should be apprised of the potential hazard to the fetus.

241 Abnormalities in the genitalia of male fetuses is an expected physiological consequence
242 of inhibition of the conversion of testosterone to DHT by 5 alpha-reductase inhibitors. These
243 results are similar to observations in male infants with genetic 5 alpha-reductase deficiency.
244 Dutasteride is absorbed through the skin. To avoid potential fetal exposure, women who are
245 pregnant or could become pregnant should not handle AVODART Soft Gelatin Capsules. If
246 contact is made with leaking capsules, the contact area should be washed immediately with soap
247 and water [see *Warnings and Precautions (5.4)*]. Dutasteride is secreted into semen. The highest
248 measured semen concentration of dutasteride in treated men was 14 ng/mL. Assuming exposure
249 of a 50-kg woman to 5 mL of semen and 100% absorption, the woman's dutasteride
250 concentration would be about 0.0175 ng/mL. This concentration is more than 100 times less than
251 concentrations producing abnormalities of male genitalia in animal studies. Dutasteride is highly
252 protein bound in human semen (greater than 96%), which may reduce the amount of dutasteride
253 available for vaginal absorption.

254 In an embryo-fetal development study in female rats, oral administration of dutasteride at
255 doses 10 times less than the maximum recommended human dose (MRHD) of 0.5 mg daily

256 resulted in abnormalities of male genitalia in the fetus (decreased anogenital distance at
257 0.05 mg/kg/day), nipple development, hypospadias, and distended preputial glands in male
258 offspring (at all doses of 0.05, 2.5, 12.5, and 30 mg/kg/day). An increase in stillborn pups was
259 observed at 111 times the MRHD, and reduced fetal body weight was observed at doses of about
260 15 times the MRHD (animal dose of 2.5 mg/kg/day). Increased incidences of skeletal variations
261 considered to be delays in ossification associated with reduced body weight were observed at
262 doses about 56 times the MRHD (animal dose of 12.5 mg/kg/day).

263 In a rabbit embryo-fetal study, doses 28- to 93-fold the MRHD (animal doses of 30, 100,
264 and 200 mg/kg/day) were administered orally during the period of major organogenesis
265 (gestation days 7 to 29) to encompass the late period of external genitalia development.
266 Histological evaluation of the genital papilla of fetuses revealed evidence of feminization of the
267 male fetus at all doses. A second embryo-fetal study in rabbits at 0.3- to 53-fold the expected
268 clinical exposure (animal doses of 0.05, 0.4, 3.0, and 30 mg/kg/day) also produced evidence of
269 feminization of the genitalia in male fetuses at all doses.

270 In an oral pre- and post-natal development study in rats, dutasteride doses of 0.05, 2.5,
271 12.5, or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia
272 (i.e., decreased anogenital distance, increased incidence of hypospadias, nipple development) of
273 male offspring occurred at 14- to 90-fold the MRHD (animal doses of 2.5 mg/kg/day or greater).
274 At 0.05-fold the expected clinical exposure (animal dose of 0.05 mg/kg/day), evidence of
275 feminization was limited to a small, but statistically significant, decrease in anogenital distance.
276 Animal doses of 2.5 to 30 mg/kg/day resulted in prolonged gestation in the parental females and
277 a decrease in time to vaginal patency for female offspring and a decrease in prostate and seminal
278 vesicle weights in male offspring. Effects on newborn startle response were noted at doses
279 greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day.

280 In an embryo-fetal development study, pregnant rhesus monkeys were exposed
281 intravenously to a dutasteride blood level comparable to the dutasteride concentration found in
282 human semen. Dutasteride was administered on gestation days 20 to 100 at doses of 400, 780,
283 1,325, or 2,010 ng/day (12 monkeys/group). The development of male external genitalia of
284 monkey offspring was not adversely affected. Reduction of fetal adrenal weights, reduction in
285 fetal prostate weights, and increases in fetal ovarian and testis weights were observed at the
286 highest dose tested in monkeys. Based on the highest measured semen concentration of
287 dutasteride in treated men (14 ng/mL), these doses represent 0.8 to 16 times the potential
288 maximum exposure of a 50-kg human female to 5 mL semen daily from a dutasteride-treated
289 man, assuming 100% absorption. (These calculations are based on blood levels of parent drug
290 which are achieved at 32 to 186 times the daily doses administered to pregnant monkeys on a
291 ng/kg basis). Dutasteride is highly bound to proteins in human semen (greater than 96%),
292 potentially reducing the amount of dutasteride available for vaginal absorption. It is not known
293 whether rabbits or rhesus monkeys produce any of the major human metabolites.

294 Estimates of exposure multiples comparing animal studies to the MRHD for
295 dutasteride are based on clinical serum concentration at steady state.

296 **8.3 Nursing Mothers**

297 AVODART is contraindicated for use in women of childbearing potential, including
298 nursing women. It is not known whether dutasteride is excreted in human milk.

299 **8.4 Pediatric Use**

300 AVODART is contraindicated for use in pediatric patients. Safety and effectiveness in
301 pediatric patients have not been established.

302 **8.5 Geriatric Use**

303 Of 2,167 male subjects treated with AVODART in 3 clinical studies, 60% were aged 65
304 years and older and 15% were aged 75 years and older. No overall differences in safety or
305 efficacy were observed between these subjects and younger subjects. Other reported clinical
306 experience has not identified differences in responses between the elderly and younger patients,
307 but greater sensitivity of some older individuals cannot be ruled out [*see Clinical Pharmacology*
308 (12.3)].

309 **8.6 Renal Impairment**

310 No dose adjustment is necessary for AVODART in patients with renal impairment [*see*
311 *Clinical Pharmacology* (12.3)].

312 **8.7 Hepatic Impairment**

313 The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied.
314 Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired
315 patients. However, in a clinical study where 60 subjects received 5 mg (10 times the therapeutic
316 dose) daily for 24 weeks, no additional adverse events were observed compared with those
317 observed at the therapeutic dose of 0.5 mg [*see Clinical Pharmacology* (12.3)].

318 **10 OVERDOSAGE**

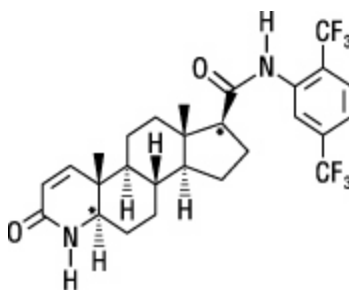
319 In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic
320 dose) for 7 days have been administered without significant safety concerns. In a clinical study,
321 daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for
322 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

323 There is no specific antidote for dutasteride. Therefore, in cases of suspected overdose,
324 symptomatic and supportive treatment should be given as appropriate, taking the long half-life of
325 dutasteride into consideration.

326 **11 DESCRIPTION**

327 AVODART is a synthetic 4-azasteroid compound that is a selective inhibitor of both the
328 type 1 and type 2 isoforms of steroid 5 alpha-reductase, an intracellular enzyme that converts
329 testosterone to DHT.

330 Dutasteride is chemically designated as (5 α ,17 β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-
331 oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is C₂₇H₃₀F₆N₂O₂,
332 representing a molecular weight of 528.5 with the following structural formula:
333



334
335

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

339 Each AVODART Soft Gelatin Capsule, administered orally, contains 0.5 mg of
340 dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated
341 hydroxytoluene. The inactive excipients in the capsule shell are ferric oxide (yellow), gelatin
342 (from certified BSE-free bovine sources), glycerin, and titanium dioxide. The soft gelatin
343 capsules are printed with edible red ink.

344 12 CLINICAL PHARMACOLOGY

345 12.1 Mechanism of Action

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

352 Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5
353 alpha-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from
354 this complex has been evaluated under in vitro and in vivo conditions and is extremely slow.
355 Dutasteride does not bind to the human androgen receptor.

356 12.2 Pharmacodynamics

357 Effect on 5 Alpha-Dihydrotestosterone and Testosterone: The maximum effect of
358 daily doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to
359 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT
360 concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with
361 dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year, 93%
362 at 2 years, and 95% at both 3 and 4 years. The median increase in serum testosterone was 19% at
363 both 1 and 2 years, 26% at 3 years, and 22% at 4 years, but the mean and median levels remained
364 within the physiologic range.

365 In patients with BPH treated with 5 mg/day of dutasteride or placebo for up to 12 weeks
366 prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were
367 significantly lower in the dutasteride group compared with placebo (784 and 5,793 pg/g,

368 respectively, $P < 0.001$). Mean prostatic tissue concentrations of testosterone were significantly
369 higher in the dutasteride group compared with placebo (2,073 and 93 pg/g, respectively,
370 $P < 0.001$).

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

376 **Effects on Other Hormones:** In healthy volunteers, 52 weeks of treatment with
377 dutasteride 0.5 mg/day ($n = 26$) resulted in no clinically significant change compared with
378 placebo ($n = 23$) in sex hormone-binding globulin, estradiol, luteinizing hormone,
379 follicle-stimulating hormone, thyroxine (free T₄), and dehydroepiandrosterone. Statistically
380 significant, baseline-adjusted mean increases compared with placebo were observed for total
381 testosterone at 8 weeks (97.1 ng/dL, $P < 0.003$) and thyroid-stimulating hormone at 52 weeks
382 (0.4 mcIU/mL, $P < 0.05$). The median percentage changes from baseline within the dutasteride
383 group were 17.9% for testosterone at 8 weeks and 12.4% for thyroid-stimulating hormone at
384 52 weeks. After stopping dutasteride for 24 weeks, the mean levels of testosterone and
385 thyroid-stimulating hormone had returned to baseline in the group of subjects with available data
386 at the visit. In patients with BPH treated with dutasteride in a large randomized, double-blind,
387 placebo-controlled study, there was a median percent increase in luteinizing hormone of 12% at
388 6 months and 19% at both 12 and 24 months.

389 **Other Effects:** Plasma lipid panel and bone mineral density were evaluated following
390 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone
391 mineral density as measured by dual energy x-ray absorptiometry compared with either placebo
392 or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low density lipoproteins,
393 high density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically
394 significant changes in adrenal hormone responses to ACTH stimulation were observed in a
395 subset population ($n = 13$) of the 1-year healthy volunteer study.

396 **12.3 Pharmacokinetics**

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

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

405 In a study of healthy subjects ($n = 26$) receiving dutasteride 0.5 mg/day for 12 months,
406 semen dutasteride concentrations averaged 3.4 ng/mL (range: 0.4 to 14 ng/mL) at 12 months
407 and, similar to serum, achieved steady-state concentrations at 6 months. On average, at

408 12 months 11.5% of serum dutasteride concentrations partitioned into semen.

409 **Metabolism and Elimination:** Dutasteride is extensively metabolized in humans. In
410 vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes.
411 Both of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride, and the
412 6,4'-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was
413 formed by CYP3A4. Dutasteride is not metabolized in vitro by human cytochrome P450
414 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and
415 CYP2E1. In human serum following dosing to steady state, unchanged dutasteride, 3 major
416 metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride), and
417 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass
418 spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl
419 additions in the 6 and 15 positions is not known. In vitro, the 4'-hydroxydutasteride and
420 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of
421 human 5 alpha-reductase. The activity of 6 β -hydroxydutasteride is comparable to that of
422 dutasteride.

423 Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there
424 was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related
425 metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine
426 (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range: 5% to 97%).

427 The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state.
428 The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day
429 for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state
430 concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of
431 dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to
432 6 months after discontinuation of treatment.

433 **Specific Populations:**

434 *Pediatric:* Dutasteride pharmacokinetics have not been investigated in subjects
435 younger than 18 years.

436 *Geriatric:* No dose adjustment is necessary in the elderly. The pharmacokinetics and
437 pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects aged between 24
438 and 87 years following administration of a single 5-mg dose of dutasteride. In this single-dose
439 study, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to
440 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in
441 men older than 70 years). Of 2,167 men treated with dutasteride in the 3 pivotal studies, 60%
442 were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy
443 were observed between these patients and younger patients.

444 *Gender:* AVODART is contraindicated in pregnancy and women of childbearing
445 potential and is not indicated for use in other women [*see Contraindications (4), Warnings and*
446 *Precautions (5.1)*]. The pharmacokinetics of dutasteride in women have not been studied.

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

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

452 *Hepatic Impairment:* The effect of hepatic impairment on dutasteride
453 pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure
454 could be higher in hepatically impaired patients.

455 **Drug Interactions:**

456 *Cytochrome P450 Inhibitors:* No clinical drug interaction studies have been
457 performed to evaluate the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics.
458 However, based on in vitro data, blood concentrations of dutasteride may increase in the
459 presence of inhibitors of CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem,
460 cimetidine, troleandomycin, and ciprofloxacin.

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

465 *Alpha Adrenergic Antagonists:* In a single-sequence, crossover study in healthy
466 volunteers, the administration of tamsulosin or terazosin in combination with AVODART had no
467 effect on the steady-state pharmacokinetics of either alpha adrenergic antagonist. Although the
468 effect of administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters
469 was not evaluated, the percent change in DHT concentrations was similar for AVODART alone
470 compared with the combination treatment.

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

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

479 *Cholestyramine:* Administration of a single 5-mg dose of AVODART followed
480 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in
481 12 normal volunteers.

482 *Digoxin:* In a study of 20 healthy volunteers, AVODART did not alter the steady-state
483 pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for
484 3 weeks.

485 *Warfarin:* In a study of 23 healthy volunteers, 3 weeks of treatment with AVODART
486 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or
487 alter the effect of warfarin on prothrombin time when administered with warfarin.

488 *Other Concomitant Therapy:* Although specific interaction studies were not
489 performed with other compounds, approximately 90% of the subjects in the 3 randomized,
490 double-blind, placebo-controlled safety and efficacy studies receiving AVODART were taking
491 other medications concomitantly. No clinically significant adverse interactions could be
492 attributed to the combination of AVODART and concurrent therapy when AVODART was
493 coadministered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors,
494 beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics,
495 nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and
496 quinolone antibiotics.

497 **13 NONCLINICAL TOXICOLOGY**

498 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

499 Carcinogenesis: A 2-year carcinogenicity study was conducted in B6C3F1 mice at
500 doses of 3, 35, 250, and 500 mg/kg/day for males and 3, 35, and 250 mg/kg/day for females; an
501 increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (290-fold
502 the MRHD of a 0.5-mg daily dose) in female mice only. Two of the 3 major human metabolites
503 have been detected in mice. The exposure to these metabolites in mice is either lower than in
504 humans or is not known.

505 In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and
506 53 mg/kg/day in males and 0.8, 6.3, and 15 mg/kg/day in females, there was an increase in
507 Leydig cell adenomas in the testes at 135-fold the MRHD (53 mg/kg/day and greater). An
508 increased incidence of Leydig cell hyperplasia was present at 52-fold the MRHD (male rat doses
509 of 7.5 mg/kg/day and greater). A positive correlation between proliferative changes in the Leydig
510 cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5
511 alpha-reductase inhibitors and is consistent with an effect on the
512 hypothalamic-pituitary-testicular axis following 5 alpha-reductase inhibition. At tumorigenic
513 doses, luteinizing hormone levels in rats were increased by 167%. In this study, the major human
514 metabolites were tested for carcinogenicity at approximately 1 to 3 times the expected clinical
515 exposure.

516 Mutagenesis: Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay
517 (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The
518 results did not indicate any genotoxic potential of the parent drug. Two major human metabolites
519 were also negative in either the Ames test or an abbreviated Ames test.

520 Impairment of Fertility: Treatment of sexually mature male rats with dutasteride at 0.1-
521 to 110-fold the MRHD (animal doses of 0.05, 10, 50, and 500 mg/kg/day for up to 31 weeks)
522 resulted in dose- and time-dependent decreases in fertility; reduced cauda epididymal (absolute)
523 sperm counts but not sperm concentration (at 50 and 500 mg/kg/day); reduced weights of the
524 epididymis, prostate, and seminal vesicles; and microscopic changes in the male reproductive
525 organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts
526 were normal at the end of a 14-week recovery period. The 5 alpha-reductase-related changes

527 consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased
528 cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate
529 and seminal vesicles. The microscopic changes were no longer present at recovery week 14 in
530 the low-dose group and were partly recovered in the remaining treatment groups. Low levels of
531 dutasteride (0.6 to 17 ng/mL) were detected in the serum of untreated female rats mated to males
532 dosed at 10, 50, or 500 mg/kg/day for 29 to 30 weeks.

533 In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5,
534 12.5, and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption, and
535 feminization of male fetuses (decreased anogenital distance) at 2- to 10-fold the MRHD (animal
536 doses of 2.5 mg/kg/day or greater). Fetal body weights were also reduced at less than 0.02-fold
537 the MRHD in rats (0.5 mg/kg/day).

538 **13.2 Animal Toxicology and/or Pharmacology**

539 Central Nervous System Toxicology Studies: In rats and dogs, repeated oral
540 administration of dutasteride resulted in some animals showing signs of non-specific, reversible,
541 centrally-mediated toxicity without associated histopathological changes at exposures 425- and
542 315-fold the expected clinical exposure (of parent drug), respectively.

543 **14 CLINICAL STUDIES**

544 **14.1 Monotherapy**

545 AVODART 0.5 mg/day (n = 2,167) or placebo (n = 2,158) was evaluated in male
546 subjects with BPH in three 2-year multicenter, placebo-controlled, double-blind studies, each
547 with 2-year open-label extensions (n = 2,340). More than 90% of the study population was
548 Caucasian. Subjects were at least 50 years of age with a serum PSA \geq 1.5 ng/mL and <10 ng/mL
549 and BPH diagnosed by medical history and physical examination, including enlarged prostate
550 (\geq 30 cc) and BPH symptoms that were moderate to severe according to the American Urological
551 Association Symptom Index (AUA-SI). Most of the 4,325 subjects randomly assigned to receive
552 either dutasteride or placebo completed 2 years of double-blind treatment (70% and 67%,
553 respectively). Most of the 2,340 subjects in the study extensions completed 2 additional years of
554 open-label treatment (71%).

555 Effect on Symptom Scores: Symptoms were quantified using the AUA-SI, a
556 questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency,
557 urgency, weak stream, straining, and nocturia) by rating on a 0 to 5 scale for a total possible
558 score of 35, with higher numerical total symptom scores representing greater severity of symptoms.
559 The baseline AUA-SI score across the 3 studies was approximately 17 units in both treatment
560 groups.

561 Subjects receiving dutasteride achieved statistically significant improvement in
562 symptoms versus placebo by Month 3 in 1 study and by Month 12 in the other 2 pivotal studies.
563 At Month 12, the mean decrease from baseline in AUA-SI total symptom scores across the
564 3 studies pooled was -3.3 units for dutasteride and -2.0 units for placebo with a mean difference
565 between the 2 treatment groups of -1.3 (range: -1.1 to -1.5 units in each of the 3 studies,

566 $P < 0.001$) and was consistent across the 3 studies. At Month 24, the mean decrease from baseline
 567 was -3.8 units for dutasteride and -1.7 units for placebo with a mean difference of -2.1 (range:
 568 -1.9 to -2.2 units in each of the 3 studies, $P < 0.001$). See Figure 1. The improvement in BPH
 569 symptoms seen during the first 2 years of double-blind treatment was maintained throughout an
 570 additional 2 years of open-label extension studies.

571 These studies were prospectively designed to evaluate effects on symptoms based on
 572 prostate size at baseline. In men with prostate volumes ≥ 40 cc, the mean decrease was -3.8 units
 573 for dutasteride and -1.6 units for placebo, with a mean difference between the 2 treatment groups
 574 of -2.2 at Month 24. In men with prostate volumes < 40 cc, the mean decrease was -3.7 units for
 575 dutasteride and -2.2 units for placebo, with a mean difference between the 2 treatment groups of
 576 -1.5 at Month 24.

577

578 **Figure 1. AUA-SI Score^a Change From Baseline (Randomized, Double-Blind,**
 579 **Placebo-Controlled Studies Pooled)**



■ Placebo	n = 2,122	n = 2,123	n = 2,123	n = 2,123
○ Dutasteride	n = 2,122	n = 2,122	n = 2,122	n = 2,122

580

581 ^a AUA-SI score ranges from 0 to 35.

582

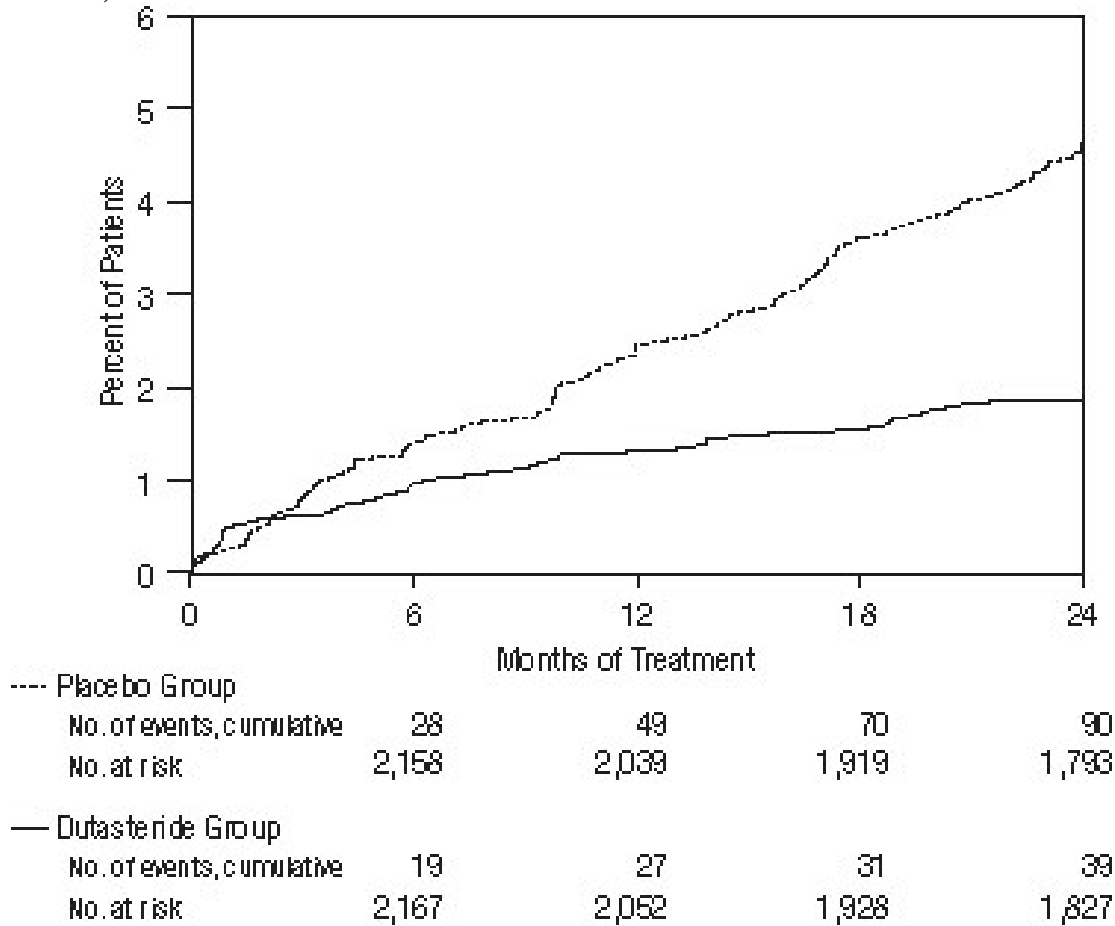
583 Effect on Acute Urinary Retention and the Need for BPH-Related Surgery:

584 Efficacy was also assessed after 2 years of treatment by the incidence of AUR requiring
 585 catheterization and BPH-related urological surgical intervention. Compared with placebo,
 586 AVODART was associated with a statistically significantly lower incidence of AUR (1.8% for

587 AVODART vs. 4.2% for placebo, $P < 0.001$; 57% reduction in risk, [95% CI: 38% to 71%]) and
 588 with a statistically significantly lower incidence of surgery (2.2% for AVODART vs. 4.1% for
 589 placebo, $P < 0.001$; 48% reduction in risk, [95% CI: 26% to 63%]). See Figures 2 and 3.

590

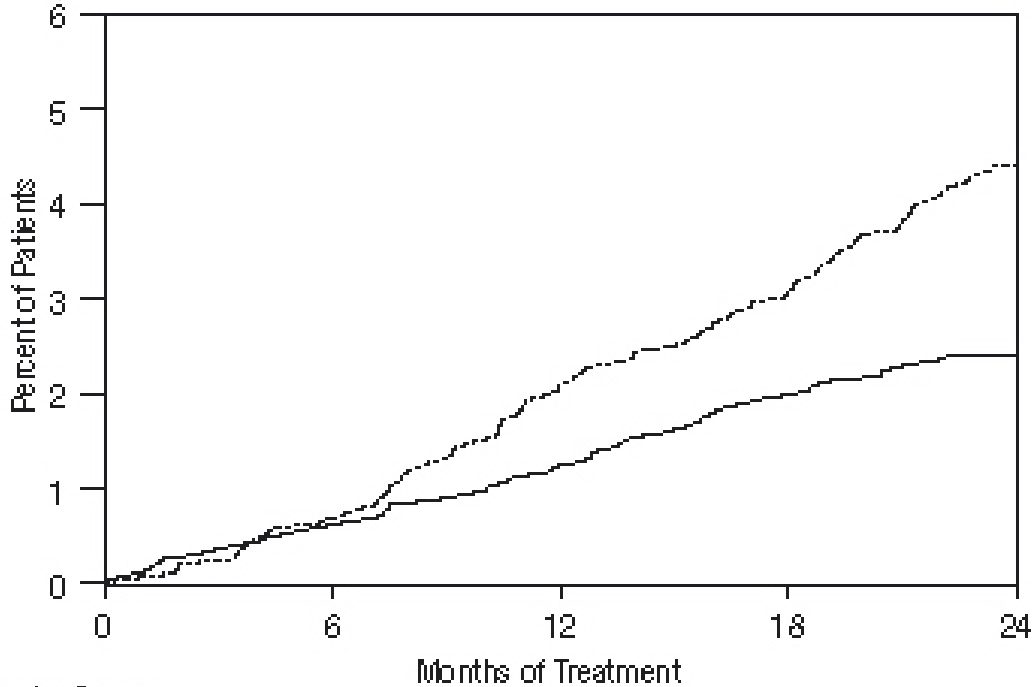
591 **Figure 2. Percent of Subjects Developing Acute Urinary Retention Over a**
 592 **24-Month Period (Randomized, Double-Blind, Placebo-Controlled Studies**
 593 **Pooled)**



594

595

596 **Figure 3. Percent of Subjects Having Surgery for Benign Prostatic Hyperplasia**
 597 **Over a 24-Month Period (Randomized, Double-Blind, Placebo-Controlled**
 598 **Studies Pooled)**



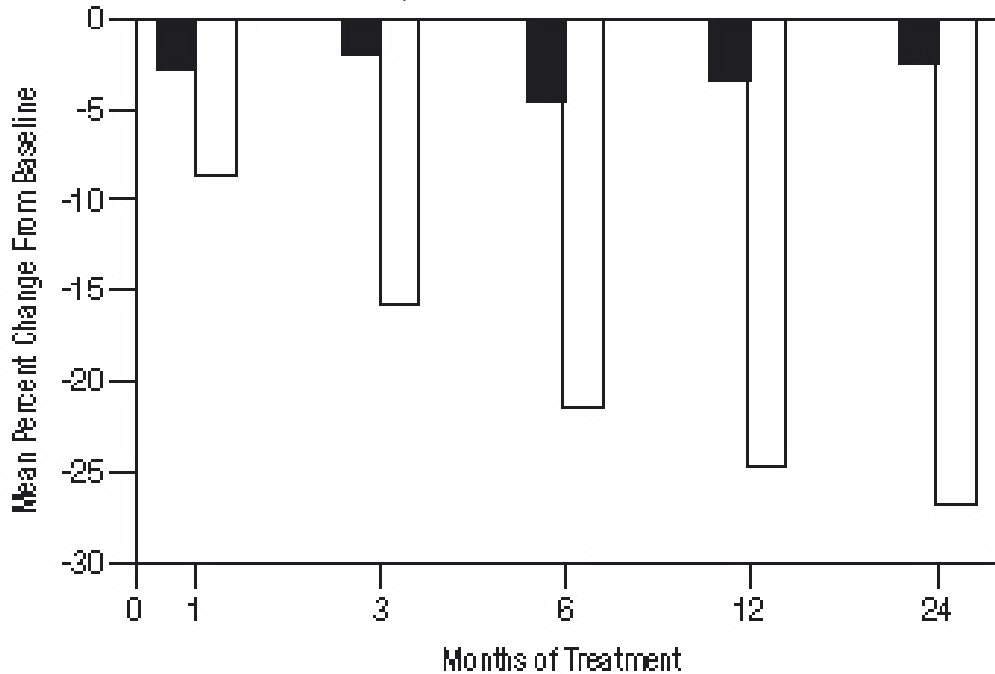
--- Placebo Group				
No. of events, cumulative	13	40	59	89
No. at risk	2,158	2,057	1,944	1,823
— Dutasteride Group				
No. of events, cumulative	12	25	39	47
No. at risk	2,167	2,064	1,944	1,846

599 **Effect on Prostate Volume:** A prostate volume of at least 30 cc measured by transrectal
 600 ultrasound was required for study entry. The mean prostate volume at study entry was
 601 approximately 54 cc.
 602

603 Statistically significant differences (AVODART versus placebo) were noted at the
 604 earliest post-treatment prostate volume measurement in each study (Month 1, Month 3, or
 605 Month 6) and continued through Month 24. At Month 12, the mean percent change in prostate
 606 volume across the 3 studies pooled was -24.7% for dutasteride and -3.4% for placebo; the mean
 607 difference (dutasteride minus placebo) was -21.3% (range: -21.0% to -21.6% in each of the
 608 3 studies, $P < 0.001$). At Month 24, the mean percent change in prostate volume across the
 609 3 studies pooled was -26.7% for dutasteride and -2.2% for placebo with a mean difference of
 610 -24.5% (range: -24.0% to -25.1% in each of the 3 studies, $P < 0.001$). See Figure 4. The reduction
 611 in prostate volume seen during the first 2 years of double-blind treatment was maintained
 612 throughout an additional 2 years of open-label extension studies.

613

614 **Figure 4. Prostate Volume Percent Change From Baseline (Randomized, Double-Blind,**
 615 **Placebo-Controlled 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

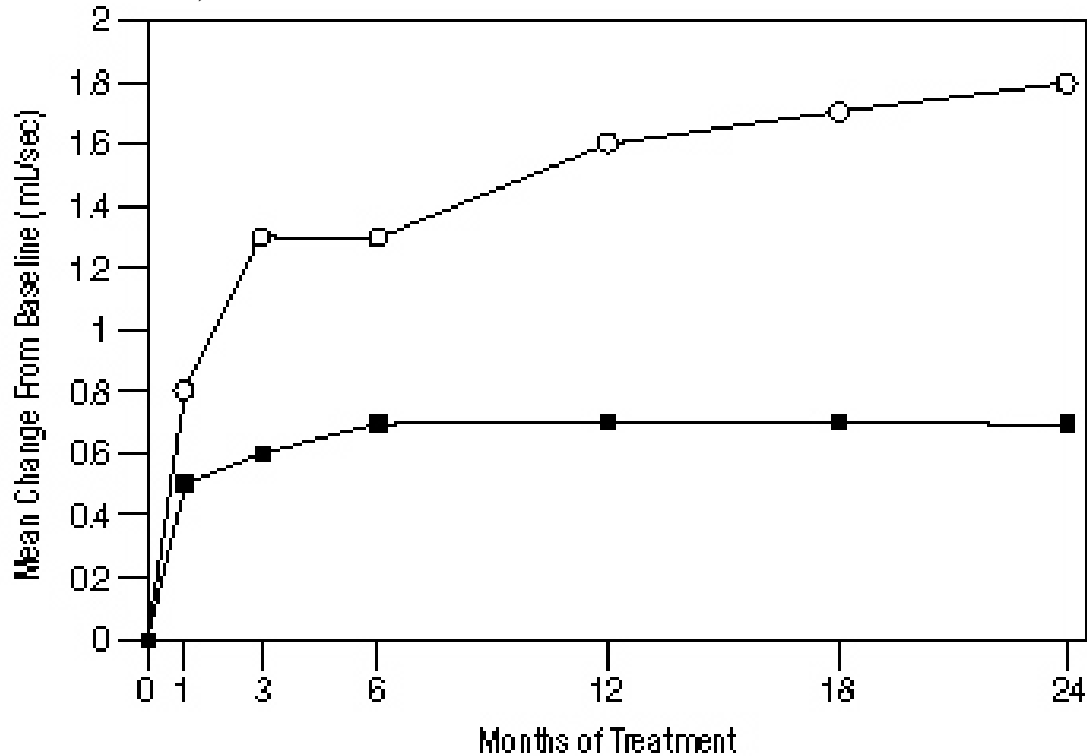
616
617

618 **Effect on Maximum Urine Flow Rate:** A mean peak urine flow rate (Q_{\max}) of
 619 ≤ 15 mL/sec was required for study entry. Q_{\max} was approximately 10 mL/sec at baseline across
 620 the 3 pivotal studies.

621 Differences between the 2 groups were statistically significant from baseline at Month 3
 622 in all 3 studies and were maintained through Month 12. At Month 12, the mean increase in Q_{\max}
 623 across the 3 studies pooled was 1.6 mL/sec for AVODART and 0.7 mL/sec for placebo; the
 624 mean difference (dutasteride minus placebo) was 0.8 mL/sec (range: 0.7 to 1.0 mL/sec in each of
 625 the 3 studies, $P < 0.001$). At Month 24, the mean increase in Q_{\max} was 1.8 mL/sec for dutasteride
 626 and 0.7 mL/sec for placebo, with a mean difference of 1.1 mL/sec (range: 1.0 to 1.2 mL/sec in
 627 each of the 3 studies, $P < 0.001$). See Figure 5. The increase in maximum urine flow rate seen
 628 during the first 2 years of double-blind treatment was maintained throughout an additional
 629 2 years of open-label extension studies.

630

631 **Figure 5. Q_{max} Change From Baseline (Randomized, Double-Blind, Placebo-Controlled**
 632 **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

633
634

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

640 **14.2 Combination With Alpha-Blocker Therapy (CombAT)**

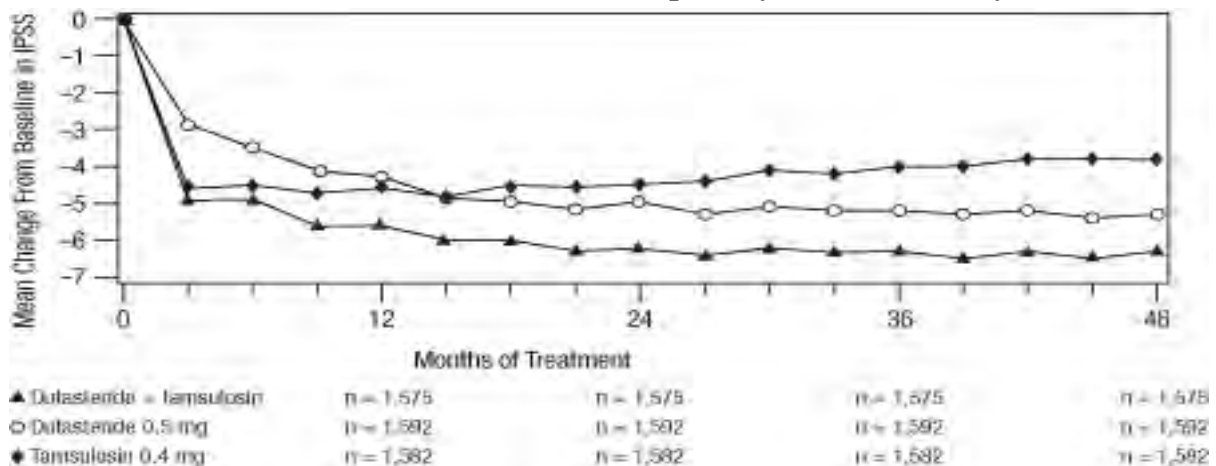
641 The efficacy of combination therapy (AVODART 0.5 mg/day plus tamsulosin
 642 0.4 mg/day, n = 1,610) was compared with AVODART alone (n = 1,623) or tamsulosin alone
 643 (n = 1,611) in a 4-year multicenter, randomized, double-blind study. Study entry criteria were
 644 similar to the double-blind, placebo-controlled monotherapy efficacy trials described above in
 645 section 14.1. Eighty-eight percent (88%) of the enrolled study population was Caucasian.
 646 Approximately 52% of subjects had previous exposure to 5 alpha-reductase inhibitor or alpha
 647 adrenergic antagonist treatment. Of the 4,844 subjects randomly assigned to receive treatment,
 648 69% of subjects in the combination group, 67% in the group receiving AVODART, and 61% in
 649 the tamsulosin group completed 4 years of double-blind treatment.

650 **Effect on Symptom Score:** Symptoms were quantified using the first 7 questions of the
 651 International Prostate Symptom Score (IPSS) (identical to the AUA-SI). The baseline score was

652 approximately 16.4 units for each treatment group. Combination therapy was statistically
 653 superior to each of the monotherapy treatments in decreasing symptom score at Month 24, the
 654 primary time point for this endpoint. At Month 24 the mean changes from baseline (\pm SD) in
 655 IPSS total symptom scores were -6.2 (\pm 7.14) for combination, -4.9 (\pm 6.81) for AVODART, and
 656 -4.3 (\pm 7.01) for tamsulosin, with a mean difference between combination and AVODART of
 657 -1.3 units ($P < 0.001$; [95% CI: -1.69, -0.86]), and between combination and tamsulosin of
 658 -1.8 units ($P < 0.001$; [95% CI: -2.23, -1.40]). A significant difference was seen by Month 9 and
 659 continued through Month 48. At Month 48 the mean changes from baseline (\pm SD) in IPSS total
 660 symptom scores were -6.3 (\pm 7.40) for combination, -5.3 (\pm 7.14) for AVODART, and -3.8
 661 (\pm 7.74) for tamsulosin, with a mean difference between combination and AVODART of
 662 -0.96 units ($P < 0.001$; [95% CI: -1.40, -0.52]), and between combination and tamsulosin of
 663 -2.5 units ($P < 0.001$; [95% CI: -2.96, -2.07]). See Figure 6.

664

665 **Figure 6. International Prostate Symptom Score Change From Baseline Over a 48-Month**
 666 **Period (Randomized, Double-Blind, Parallel Group Study [CombAT Study])**



667

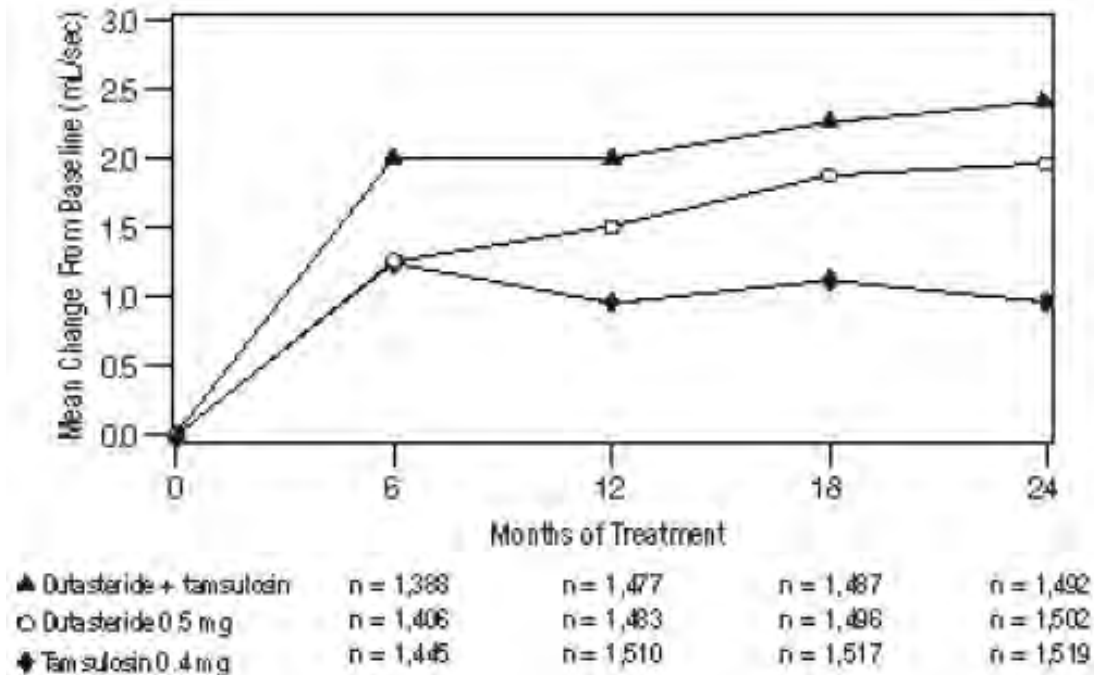
668

669 Effect on Acute Urinary Retention or the Need for BPH-Related Surgery: After
 670 4 years of treatment, combination therapy with AVODART and tamsulosin did not provide
 671 benefit over monotherapy with AVODART in reducing the incidence of AUR or BPH-related
 672 surgery.

673 Effect on Maximum Urine Flow Rate: The baseline Q_{max} was approximately
 674 10.7 mL/sec for each treatment group. Combination therapy was statistically superior to each of
 675 the monotherapy treatments in increasing Q_{max} at Month 24, the primary time point for this
 676 endpoint. At Month 24, the mean increases from baseline (\pm SD) in Q_{max} were 2.4 (\pm 5.26) mL/sec
 677 for combination, 1.9 (\pm 5.10) mL/sec for AVODART, and 0.9 (\pm 4.57) mL/sec for tamsulosin,
 678 with a mean difference between combination and AVODART of 0.5 mL/sec ($P = 0.003$; [95%
 679 CI: 0.17, 0.84]), and between combination and tamsulosin of 1.5 mL/sec ($P < 0.001$; [95% CI:
 680 1.19, 1.86]). This difference was seen by Month 6 and continued through Month 24. See
 681 Figure 7.

682 The additional improvement in Q_{max} of combination therapy over monotherapy with
 683 AVODART was no longer statistically significant at Month 48.

684
 685 **Figure 7. Q_{max} Change From Baseline Over a 24-Month Period (Randomized, Double-**
 686 **Blind, Parallel Group Study [CombAT Study])**



687
 688
 689 **Effect on Prostate Volume:** The mean prostate volume at study entry was
 690 approximately 55 cc. At Month 24, the primary time point for this endpoint, the mean percent
 691 changes from baseline (\pm SD) in prostate volume were -26.9% (\pm 22.57) for combination therapy,
 692 -28.0% (\pm 24.88) for AVODART, and 0% (\pm 31.14) for tamsulosin, with a mean difference
 693 between combination and AVODART of 1.1% ($P = NS$; [95% CI: -0.6, 2.8]), and between
 694 combination and tamsulosin of -26.9% ($P < 0.001$; [95% CI: -28.9, -24.9]). Similar changes were
 695 seen at Month 48: -27.3% (\pm 24.91) for combination therapy, -28.0% (\pm 25.74) for AVODART,
 696 and +4.6% (\pm 35.45) for tamsulosin.

697 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

703 Dutasteride is absorbed through the skin. AVODART Capsules should not be handled by
 704 women who are pregnant or who could become pregnant because of the potential for absorption
 705 of dutasteride and the subsequent potential risk to a developing male fetus [see Warnings and

706 *Precautions (5.4)]*.

707 **17 PATIENT COUNSELING INFORMATION**

708 See FDA-approved patient labeling (Patient Information).

709 **17.1 PSA Monitoring**

710 Physicians should inform patients that AVODART reduces serum PSA levels by
711 approximately 50% within 3 to 6 months of therapy, although it may vary for each individual.
712 For patients undergoing PSA screening, increases in PSA levels while on treatment with
713 AVODART may signal the presence of prostate cancer and should be evaluated by a healthcare
714 provider [*see Warnings and Precautions (5.1)]*.

715 **17.2 Increased Risk of High-grade Prostate Cancer**

716 Physicians should inform patients that there was an increase in high-grade prostate cancer
717 in men treated with 5 alpha-reductase inhibitors (which are indicated for BPH treatment),
718 including AVODART, compared with those treated with placebo in studies looking at the use of
719 these drugs to reduce the risk of prostate cancer [*see Indications and Usage (1.3), Warnings and*
720 *Precautions (5.2), Adverse Reactions (6.1)]*.

721 **17.3 Exposure of Women—Risk to Male Fetus**

722 Physicians should inform patients that AVODART Capsules should not be handled by a
723 woman who is pregnant or who could become pregnant because of the potential for absorption of
724 dutasteride and the subsequent potential risk to a developing male fetus. Dutasteride is absorbed
725 through the skin and could result in unintended fetal exposure. If a pregnant woman or woman of
726 childbearing potential comes in contact with leaking AVODART Capsules, the contact area
727 should be washed immediately with soap and water [*see Warnings and Precautions (5.4), Use in*
728 *Specific Populations (8.1)]*.

729 **17.4 Blood Donation**

730 Physicians should inform men treated with AVODART that they should not donate blood
731 until at least 6 months following their last dose to prevent pregnant women from receiving
732 dutasteride through blood transfusion [*see Warnings and Precautions (5.5)]*. Serum levels of
733 dutasteride are detectable for 4 to 6 months after treatment ends [*see Clinical Pharmacology*
734 *(12.3)]*.

735

736



737 **GlaxoSmithKline**

738 GlaxoSmithKline

739 Research Triangle Park, NC 27709

740

741 Manufactured by Catalent Pharma Solutions, Beinheim, France for

742 GlaxoSmithKline, Research Triangle Park, NC 27709

743

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PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

748

749

Patient Information

750

751

**AVODART[®] (av' ō dart)
(dutasteride) Capsules**

752

753

754

AVODART is for use by men only.

755

756 Read this patient information before you start taking AVODART and each time you
757 get a refill. There may be new information. This information does not take the place
758 of talking with your healthcare provider about your medical condition or your
759 treatment.

760

What is AVODART?

761

762 AVODART is a prescription medicine that contains dutasteride. AVODART is used to
763 treat the symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged
764 prostate to:

765

- Improve symptoms
- Reduce the risk of acute urinary retention (a complete blockage of urine flow)
- Reduce the risk of the need for BPH-related surgery

766

767

768

Who should NOT take AVODART?

769

Do Not Take AVODART if you are:

770

- pregnant or could become pregnant. AVODART may harm your unborn baby.
771 Pregnant women should not touch AVODART Capsules. If a woman who is
772 pregnant with a male baby gets enough AVODART in her body by swallowing or
773 touching AVODART, the male baby may be born with sex organs that are not
774 normal. If a pregnant woman or woman of childbearing potential comes in
775 contact with leaking AVODART Capsules, the contact area should be washed
776 immediately with soap and water.

777

- a child or a teenager.
- allergic to dutasteride or any of the ingredients in AVODART. See the end of this
778 leaflet for a complete list of ingredients in AVODART.

779

- allergic to other 5 alpha-reductase inhibitors, for example, PROSCAR
780 (finasteride) Tablets.

781

782

What should I tell my healthcare provider before taking AVODART?

Before you take AVODART, tell your healthcare provider if you:

- have liver problems

783

784 Tell your healthcare provider about all the medicines you take, including
785 prescription and non-prescription medicines, vitamins, and herbal supplements.

786 AVODART and other medicines may affect each other, causing side effects.

787 AVODART may affect the way other medicines work, and other medicines may

788 affect how AVODART works.

789

790 Know the medicines you take. Keep a list of them to show your healthcare provider
791 and pharmacist when you get a new medicine.

792

How should I take AVODART?

794 • Take 1 AVODART capsule once a day.

795 • Swallow AVODART capsules whole. Do not crush, chew, or open AVODART
796 capsules because the contents of the capsule may irritate your lips, mouth, or
797 throat.

798 • You can take AVODART with or without food.

799 • If you miss a dose, you may take it later that day. Do not make up the missed
800 dose by taking 2 doses the next day.

801

What should I avoid while taking AVODART?

- You should not donate blood while taking AVODART or for 6 months after you have stopped AVODART. This is important to prevent pregnant women from receiving AVODART through blood transfusions.

802

What are the possible side effects of AVODART?

AVODART may cause serious side effects, including:

804 • **Rare and serious allergic reactions, including:**

805 • swelling of your face, tongue, or throat

806 • serious skin reactions, such as skin peeling

807 Get medical help right away if you have these serious allergic reactions.

808 • **Higher chance of a more serious form of prostate cancer.**

809

810 The most common side effects of AVODART include:

811 • trouble getting or keeping an erection (impotence)

812 • a decrease in sex drive (libido)

- 813 • ejaculation problems
814 • enlarged or painful breasts. If you notice breast lumps or nipple discharge, you
815 should talk to your healthcare provider.

AVODART has been shown to reduce sperm count, semen volume, and sperm movement. However, the effect of AVODART on male fertility is not known.

816
817 **Prostate Specific Antigen (PSA) Test:** Your healthcare provider may check you
818 for other prostate problems, including prostate cancer before you start and while
819 you take AVODART. A blood test called PSA (prostate-specific antigen) is
820 sometimes used to see if you might have prostate cancer. AVODART will reduce the
821 amount of PSA measured in your blood. Your healthcare provider is aware of this
822 effect and can still use PSA to see if you might have prostate cancer. Increases in
823 your PSA levels while on treatment with AVODART (even if the PSA levels are in the
824 normal range) should be evaluated by your healthcare provider.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects with AVODART. For more information, ask your healthcare provider or pharmacist.

825
826 Call your doctor for medical advice about side effects. You may report side effects
827 to FDA at 1-800-FDA-1088.

828
829 **How should I store AVODART?**

- 830 • Store AVODART Capsules at room temperature (59°F to 86°F or 15°C to 30°C).
831 • AVODART Capsules may become deformed and/or discolored if kept at high
832 temperatures.
833 • Do not use AVODART if your capsules are deformed, discolored, or leaking.
834 • Safely throw away medicine that is no longer needed.

Keep AVODART and all medicines out of the reach of children.

Medicines are sometimes prescribed for purposes other than those listed in a patient leaflet. Do not use AVODART for a condition for which it was not prescribed. Do not give AVODART to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about AVODART. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about AVODART that is written for health professionals.

835

836 For more information, go to www.AVODART.com or call 1-888-825-5249.

What are the ingredients in AVODART?

Active ingredient: dutasteride.

837 **Inactive ingredients:** butylated hydroxytoluene, ferric oxide (yellow), gelatin

838 (from certified BSE-free bovine sources), glycerin, mono-di-glycerides of

839 caprylic/capric acid, titanium dioxide, and edible red ink.

How does AVODART work?

Prostate growth is caused by a hormone in the blood called dihydrotestosterone (DHT). AVODART lowers DHT production in the body, leading to shrinkage of the enlarged prostate in most men. While some men have fewer problems and symptoms after 3 months of treatment with AVODART, a treatment of period of at least 6 months is usually necessary to see if AVODART will work for you.

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