

## 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, Combination With Alpha-Blocker (1.2) 6/2008  
Dosage and Administration, Combination With Alpha-Blocker (2.2) 6/2008

#### INDICATIONS AND USAGE

AVODART, a 5 $\alpha$ -reductase inhibitor, is 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-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate. (1.2)

#### 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, 5.1, 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

- Women who are pregnant or may become pregnant should not handle AVODART Capsules. (5.1, 8.1)
- Patients should be assessed to rule out other urological diseases, including prostate cancer, prior to prescribing AVODART. (5.2)
- AVODART reduces total serum prostate-specific antigen concentration by approximately 50%. (5.3)
- Patients should not donate blood until 6 months after their last dose. (5.4)

#### 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](http://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: 6/2008

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\*Sections or subsections omitted from the full prescribing information are not listed.

## 1 FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Monotherapy

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

- improve symptoms,
- reduce the risk of acute urinary retention (AUR), and

- reduce the risk of the need for BPH-related surgery.

## 1.2 Combination With Alpha-Blocker

AVODART in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

## 2 DOSAGE AND ADMINISTRATION

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

### 2.1 Monotherapy

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

### 2.2 Combination With Alpha-Blocker

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

### 2.3 Dosage Adjustment in Specific Populations

No dose adjustment is necessary for patients with renal impairment or for the elderly [see *Clinical Pharmacology (12.3)*]. Due to the absence of data in patients with hepatic impairment, no dosage recommendation can be made [see *Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

AVODART is contraindicated for use in:

- **Pregnancy.** Dutasteride inhibits the activity of 5 $\alpha$ -reductase, which prevents conversion of testosterone to dihydrotestosterone, a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited development of male fetus external genitalia. Therefore, AVODART may cause fetal harm when administered to a pregnant woman. If AVODART is used during pregnancy or if the patient becomes pregnant while taking AVODART, the patient should be apprised of the potential hazard to the fetus [see *Warnings and Precautions (5.1), Use in Specific Populations (8.1)*].
- Women of childbearing potential [see *Warnings and Precautions (5.1), Use in Specific Populations (8.1)*].
- Pediatric patients [see *Use in Specific Populations (8.4)*].
- Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to AVODART or other 5 $\alpha$ -reductase inhibitors.

## 44 **5 WARNINGS AND PRECAUTIONS**

### 45 **5.1 Exposure of Women—Risk to Male Fetus**

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

### 51 **5.2 Evaluation for Other Urological Diseases**

52 Lower urinary tract symptoms of BPH can be indicative of other urological diseases,  
53 including prostate cancer. Patients should be assessed to rule out prostate cancer and other  
54 urological diseases prior to treatment with AVODART and periodically thereafter. Patients with  
55 a large residual urinary volume and/or severely diminished urinary flow may not be good  
56 candidates for 5 $\alpha$ -reductase inhibitor therapy and should be carefully monitored for obstructive  
57 uropathy.

### 58 **5.3 Effects on Prostate-Specific Antigen (PSA) and the Use of PSA in Prostate** 59 **Cancer Detection**

60 Dutasteride reduces total serum PSA concentration by approximately 40% following  
61 3 months of treatment and by approximately 50% following 6, 12, and 24 months of treatment.  
62 This decrease is predictable over the entire range of PSA values, although it may vary in  
63 individual patients. Therefore, for interpretation of serial PSAs in a man taking AVODART, a  
64 new baseline PSA concentration should be established after 3 to 6 months of treatment, and this  
65 new value should be used to assess potentially cancer-related changes in PSA. To interpret an  
66 isolated PSA value in a man treated with AVODART for 6 months or more, the PSA value  
67 should be doubled for comparison with normal values in untreated men.

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

71 Coadministration of tamsulosin with dutasteride resulted in similar changes to total PSA  
72 as dutasteride monotherapy.

### 73 **5.4 Blood Donation**

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

### 77 **5.5 Effect on Semen Characteristics**

78 The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal  
79 volunteers aged 18 to 52 (n = 27 dutasteride, n = 23 placebo) throughout 52 weeks of treatment  
80 and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from  
81 baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%,  
82 respectively, in the dutasteride group when adjusted for changes from baseline in the placebo  
83 group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of

84 follow-up, the mean percent change in total sperm count in the dutasteride group remained 23%  
85 lower than baseline. While mean values for all semen parameters at all time-points remained  
86 within the normal ranges and did not meet predefined criteria for a clinically significant change  
87 (30%), 2 subjects in the dutasteride group had decreases in sperm count of greater than 90%  
88 from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical  
89 significance of dutasteride's effect on semen characteristics for an individual patient's fertility is  
90 not known.

## 91 **6 ADVERSE REACTIONS**

### 92 **6.1 Clinical Trials Experience**

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

#### 96 Monotherapy:

- 97 • The most common adverse reactions reported in subjects receiving AVODART were  
98 impotence, decreased libido, breast disorders (including breast enlargement and tenderness),  
99 and ejaculation disorders.
- 100 • Study withdrawal due to adverse reactions occurred in 4% of subjects receiving AVODART  
101 and 3% of subjects receiving placebo. The most common adverse reaction leading to study  
102 withdrawal was impotence (1%).

103 Over 4,300 male subjects with BPH were randomly assigned to receive placebo or  
104 0.5-mg daily doses of AVODART in 3 identical 2-year, placebo-controlled, double-blind,  
105 Phase 3 treatment studies, each with 2-year open-label extensions. During the double-blind  
106 treatment period, 2,167 male subjects were exposed to AVODART, including 1,772 exposed for  
107 1 year and 1,510 exposed for 2 years. When including the open-label extensions, 1,009 male  
108 subjects were exposed to AVODART for 3 years and 812 were exposed for 4 years. The  
109 population was aged 47 to 94 years (mean age, 66 years) and greater than 90% Caucasian.  
110 Table 1 summarizes clinical adverse reactions reported in at least 1% of subjects receiving  
111 AVODART and at a higher incidence than subjects receiving placebo.  
112

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

Adverse Reactions AVODART (n) Placebo (n)	Adverse Reaction Time of 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 AVODART Placebo	4.7% 1.7%	1.4% 1.5%	1.0% 0.5%	0.8% 0.9%
Decreased libido AVODART Placebo	3.0% 1.4%	0.7% 0.6%	0.3% 0.2%	0.3% 0.1%
Ejaculation disorders AVODART Placebo	1.4% 0.5%	0.5% 0.3%	0.5% 0.1%	0.1% 0.0%
Breast disorders* AVODART Placebo	0.5% 0.2%	0.8% 0.3%	1.1% 0.3%	0.6% 0.1%

116 \*Includes breast tenderness and breast enlargement.

117  
 118 *Long-Term Treatment (Up to 4 Years):* There is no evidence of increased  
 119 drug-related sexual adverse reactions (impotence, decreased libido, and ejaculation disorder) or  
 120 breast disorders with increased duration of treatment. The relationship between long-term use of  
 121 AVODART and male breast neoplasia is currently unknown.

122 **Combination with Alpha-Blocker Therapy (CombAT):**

- 123 • The most common adverse reactions reported in subjects receiving combination therapy  
 124 (AVODART plus tamsulosin) were impotence, decreased libido, breast disorders (including  
 125 breast enlargement and tenderness), ejaculation disorders, and dizziness. Over 2 years of  
 126 treatment, drug-related ejaculation disorders occurred more frequently in subjects receiving  
 127 combination therapy (9%) compared to AVODART (2%) or tamsulosin (3%) as  
 128 monotherapy.
- 129 • Study withdrawal due to adverse reactions occurred in 5% of subjects receiving combination  
 130 therapy (AVODART plus tamsulosin) and 3% of subjects receiving AVODART or  
 131 tamsulosin as monotherapy. The most common adverse reaction leading to study withdrawal  
 132 in subjects receiving combination therapy was impotence (1%).

133 Over 4,800 male subjects with BPH were randomly assigned to receive either 0.5-mg  
 134 AVODART, 0.4-mg tamsulosin, or combination therapy (0.5-mg AVODART plus 0.4-mg

135 tamsulosin) administered once daily in a 4-year double-blind study. Adverse reaction  
 136 information over the first 2 years of treatment is presented below; information for years 2 to 4 is  
 137 not yet available as the study is ongoing. During the first 2 years, 1,623 subjects received  
 138 monotherapy with AVODART; 1,611 subjects received monotherapy with tamsulosin; and  
 139 1,610 subjects received combination therapy. The population was aged 49 to 88 years (mean age,  
 140 66 years) and 88% Caucasian. Table 2 summarizes adverse reactions reported in at least 1% of  
 141 subjects in any treatment group.

142 **Table 2. Adverse Reactions Reported Over a 24-Month Period in  $\geq 1\%$  of Subjects in**  
 143 **Any Treatment Group (CombAT) by Time of Onset**  
 144

Adverse Reactions	Adverse Reaction Time of Onset			
	Month 0-6 (n = 1,610)	Month 7-12 (n = 1,524)	Month 13-18 (n = 1,424)	Month 19-24 (n = 1,345)
Combination (n)*	(n = 1,623)	(n = 1,547)	(n = 1,457)	(n = 1,378)
AVODART (n)	(n = 1,611)	(n = 1,542)	(n = 1,468)	(n = 1,363)
Tamsulosin(n)				
Impotence				
Combination	5.5%	1.2%	0.8%	0.3%
AVODART	3.9%	1.2%	0.6%	0.7%
Tamsulosin	2.7%	0.8%	0.4%	0.4%
Decreased libido				
Combination	4.5%	0.9%	0.4%	<0.1%
AVODART	3.3%	0.6%	0.7%	0.2%
Tamsulosin	1.9%	0.6%	0.4%	0.2%
Ejaculation disorders				
Combination	7.6%	1.6%	0.4%	<0.1%
AVODART	1.1%	0.6%	0.1%	0.1%
Tamsulosin	2.2%	0.5%	0.4%	0.1%
Breast disorders <sup>†</sup>				
Combination	1.0%	1.1%	0.7%	0.3%
AVODART	0.9%	1.0%	0.8%	0.5%
Tamsulosin	0.4%	0.4%	0.2%	0.1%
Dizziness				
Combination	1.1%	0.4%	0.2%	0.0%
AVODART	0.4%	0.2%	<0.1%	<0.1%
Tamsulosin	0.9%	0.5%	0.3%	0.1%

145 \*Combination = AVODART 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

146 <sup>†</sup>Includes breast tenderness and breast enlargement.

147

148 **6.2 Postmarketing Experience**

149 The following adverse reactions have been identified during postapproval use of  
150 AVODART. Because these reactions are reported voluntarily from a population of uncertain  
151 size, it is not always possible to reliably estimate their frequency or establish a causal  
152 relationship to drug exposure. These reactions have been chosen for inclusion due to a  
153 combination of their seriousness, frequency of reporting, or potential causal connection to  
154 AVODART.

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

157 **7 DRUG INTERACTIONS**

158 **7.1 Cytochrome P450 3A Inhibitors**

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

164 **7.2 Alpha-Adrenergic Blocking Agents**

165 The administration of AVODART in combination with tamsulosin or terazosin has no  
166 effect on the steady-state pharmacokinetics of either alpha-adrenergic blocker. The effect of  
167 administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters has not  
168 been evaluated.

169 **7.3 Calcium Channel Antagonists**

170 Coadministration of verapamil or diltiazem decreases dutasteride clearance and leads to  
171 increased exposure to dutasteride. The change in dutasteride exposure is not considered to be  
172 clinically significant. No dose adjustment is recommended [*see Clinical Pharmacology (12.3)*].

173 **7.4 Cholestyramine**

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

177 **7.5 Digoxin**

178 AVODART does not alter the steady-state pharmacokinetics of digoxin when  
179 administered concomitantly at a dose of 0.5 mg/day for 3 weeks [*see Clinical Pharmacology*  
180 *(12.3)*].

181 **7.6 Warfarin**

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

185 **8 USE IN SPECIFIC POPULATIONS**

186 **8.1 Pregnancy**



187           Pregnancy Category X. [See Contraindications (4)]. AVODART is contraindicated for  
188 use in women of childbearing potential and during pregnancy. AVODART is a 5 $\alpha$ -reductase  
189 inhibitor that prevents conversion of testosterone to dihydrotestosterone (DHT), a hormone  
190 necessary for normal development of male genitalia. In animal reproduction and developmental  
191 toxicity studies, dutasteride inhibited normal development of external genitalia in male fetuses.  
192 Therefore, AVODART may cause fetal harm when administered to a pregnant woman. If  
193 AVODART is used during pregnancy or if the patient becomes pregnant while taking  
194 AVODART, the patient should be apprised of the potential hazard to the fetus.

195           Abnormalities in the genitalia of male fetuses is an expected physiological consequence  
196 of inhibition of the conversion of testosterone to 5 $\alpha$ -dihydrotestosterone (DHT) by 5 $\alpha$ -reductase  
197 inhibitors. These results are similar to observations in male infants with genetic 5 $\alpha$ -reductase  
198 deficiency. Dutasteride is absorbed through the skin. To avoid potential fetal exposure, women  
199 who are pregnant or may become pregnant should not handle AVODART Soft Gelatin Capsules.  
200 If contact is made with leaking capsules, the contact area should be washed immediately with  
201 soap and water. Dutasteride is secreted into male semen. The highest measured semen  
202 concentration of dutasteride in treated men was 14 ng/mL. Assuming exposure of a 50-kg  
203 woman to 5 mL of semen and 100% absorption, the woman's dutasteride concentration would be  
204 about 0.175 ng/mL. This concentration is more than 100 times less than concentrations  
205 producing abnormalities of male genitalia in animal studies. Dutasteride is highly protein bound  
206 in human semen (>96%), which may reduce the amount of dutasteride available for vaginal  
207 absorption [see Warnings and Precautions (5.1)].

208           In an embryo-fetal development study in female rats, oral administration of dutasteride  
209 at doses 10 times less than the maximum recommended human dose (MRHD) resulted in  
210 abnormalities of male genitalia in the fetus, and nipple development, hypospadias, and  
211 distended preputial glands in male offspring. An increase in stillborn pups was observed at  
212 111 times the MRHD, and reduced fetal body weight was observed at doses  $\geq$ 15 times the  
213 MRHD. Increased incidences of skeletal variations considered to be delays in ossification  
214 associated with reduced body weight were observed at doses  $\geq$ 56 times the MRHD.  
215 Abnormalities of male genitalia were also observed in an oral pre- and post-natal development  
216 study in rats and in 2 embryo-fetal studies in rabbits at one-third the MRHD.

217           In an embryo-fetal development study, pregnant rhesus monkeys were exposed  
218 intravenously to a dutasteride blood level comparable to the dutasteride concentration found  
219 in human semen. The development of male external genitalia of monkey offspring was not  
220 adversely affected. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and  
221 increases in fetal ovarian and testis weights were observed in monkeys [see Nonclinical  
222 Toxicology (13.3)].

### 223 **8.3 Nursing Mothers**

224           AVODART should not be used by nursing women. It is not known whether dutasteride is  
225 excreted in human milk.

### 226 **8.4 Pediatric Use**



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

### 229 **8.5 Geriatric Use**

230 Of 2,167 male subjects treated with AVODART in 3 clinical studies, 60% were 65 and  
231 over and 15% were 75 and over. No overall differences in safety or efficacy were observed  
232 between these subjects and younger subjects. Other reported clinical experience has not  
233 identified differences in responses between the elderly and younger patients [see *Clinical*  
234 *Pharmacology (12.3)*].

### 235 **8.6 Renal Impairment**

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

### 238 **8.7 Hepatic Impairment**

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

## 244 **10 OVERDOSAGE**

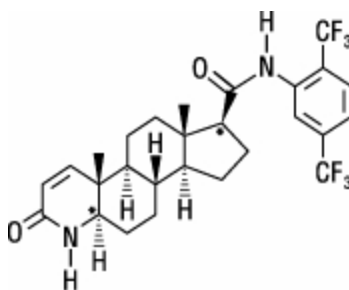
245 In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic  
246 dose) for 7 days have been administered without significant safety concerns. In a clinical study,  
247 daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for  
248 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

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

## 252 **11 DESCRIPTION**

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

256 Dutasteride is chemically designated as (5 $\alpha$ ,17 $\beta$ )-N-{2,5 bis(trifluoromethyl)phenyl}-3-  
257 oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is C<sub>27</sub>H<sub>30</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub>,  
258 representing a molecular weight of 528.5 with the following structural formula:  
259



260  
261

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

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

## 270 **12 CLINICAL PHARMACOLOGY**

### 271 **12.1 Mechanism of Action**

272 Dutasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT is  
273 the androgen primarily responsible for the initial development and subsequent enlargement of the  
274 prostate gland. Testosterone is converted to DHT by the enzyme 5 $\alpha$ -reductase, which exists as  
275 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive  
276 tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and  
277 liver.

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

### 282 **12.2 Pharmacodynamics**

283 Effect on 5 $\alpha$ -Dihydrotestosterone and Testosterone: The maximum effect of daily  
284 doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to  
285 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT  
286 concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with  
287 dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year, 93%  
288 at 2 years, and 95% at both 3 and 4 years. The median increase in serum testosterone was 19% at  
289 both 1 and 2 years, 26% at 3 years, and 22% at 4 years, but the mean and median levels remained  
290 within the physiologic range.

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

294 respectively,  $p < 0.001$ ). Mean prostatic tissue concentrations of testosterone were significantly  
295 higher in the dutasteride group compared with placebo (2,073 and 93 pg/g, respectively,  
296  $p < 0.001$ ).

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

302 **Effects on Other Hormones:** In healthy volunteers, 52 weeks of treatment with  
303 dutasteride 0.5 mg/day ( $n = 26$ ) resulted in no clinically significant change compared with  
304 placebo ( $n = 23$ ) in sex hormone-binding globulin, estradiol, luteinizing hormone,  
305 follicle-stimulating hormone, thyroxine (free T<sub>4</sub>), and dehydroepiandrosterone. Statistically  
306 significant, baseline-adjusted mean increases compared with placebo were observed for total  
307 testosterone at 8 weeks (97.1 ng/dL,  $p < 0.003$ ) and thyroid-stimulating hormone at 52 weeks  
308 (0.4 mcIU/mL,  $p < 0.05$ ). The median percentage changes from baseline within the dutasteride  
309 group were 17.9% for testosterone at 8 weeks and 12.4% for thyroid-stimulating hormone at  
310 52 weeks. After stopping dutasteride for 24 weeks, the mean levels of testosterone and  
311 thyroid-stimulating hormone had returned to baseline in the group of subjects with available data  
312 at the visit. In patients with BPH treated with dutasteride in a large randomized, double-blind,  
313 placebo-controlled study, there was a median percent increase in luteinizing hormone of 12% at  
314 6 months and 19% at both 12 and 24 months.

315 **Other Effects:** Plasma lipid panel and bone mineral density were evaluated following  
316 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone  
317 mineral density as measured by dual energy x-ray absorptiometry compared with either placebo  
318 or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low density lipoproteins,  
319 high density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically  
320 significant changes in adrenal hormone responses to ACTH stimulation were observed in a  
321 subset population ( $n = 13$ ) of the 1-year healthy volunteer study.

### 322 **12.3 Pharmacokinetics**

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

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

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

334 11.5% of serum dutasteride concentrations partitioned into semen.

335 **Metabolism and Elimination:** Dutasteride is extensively metabolized in humans. In  
336 vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes.  
337 Both of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride, and the  
338 6,4'-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was  
339 formed by CYP3A4. Dutasteride is not metabolized in vitro by human cytochrome P450  
340 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and  
341 CYP2E1. In human serum following dosing to steady state, unchanged dutasteride, 3 major  
342 metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride), and  
343 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass  
344 spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl  
345 additions in the 6 and 15 positions is not known. In vitro, the 4'-hydroxydutasteride and  
346 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of  
347 human 5 $\alpha$ -reductase. The activity of 6 $\beta$ -hydroxydutasteride is comparable to that of dutasteride.

348 Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there  
349 was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related  
350 metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine  
351 (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range, 5% to 97%).

352 The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state.  
353 The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day  
354 for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state  
355 concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of  
356 dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to  
357 6 months after discontinuation of treatment.

358 **Specific Populations: Pediatric:** Dutasteride pharmacokinetics have not been  
359 investigated in subjects younger than 18 years.

360 **Geriatric:** No dose adjustment is necessary in the elderly. The pharmacokinetics and  
361 pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects aged between 24  
362 and 87 years following administration of a single 5-mg dose of dutasteride. In this single-dose  
363 study, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to  
364 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in  
365 men older than 70 years). Of 2,167 men treated with dutasteride in the 3 pivotal studies, 60%  
366 were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy  
367 were observed between these patients and younger patients.

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

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

372 **Renal Impairment:** The effect of renal impairment on dutasteride pharmacokinetics  
373 has not been studied. However, less than 0.1% of a steady-state 0.5-mg dose of dutasteride is

374 recovered in human urine, so no adjustment in dosage is anticipated for patients with renal  
375 impairment.

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

379 Drug Interactions: No clinical drug interaction studies have been performed to evaluate  
380 the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics. However, based on in  
381 vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of  
382 CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, troleandomycin,  
383 and ciprofloxacin.

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

388 *Alpha-Adrenergic Blocking Agents:* In a single-sequence, crossover study in healthy  
389 volunteers, the administration of tamsulosin or terazosin in combination with AVODART had no  
390 effect on the steady-state pharmacokinetics of either alpha-adrenergic blocker. Although the  
391 effect of administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters  
392 was not evaluated, the percent change in DHT concentrations was similar for AVODART alone  
393 compared with the combination treatment.

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

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

402 *Cholestyramine:* Administration of a single 5-mg dose of AVODART followed  
403 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in  
404 12 normal volunteers.

405 *Digoxin:* In a study of 20 healthy volunteers, AVODART did not alter the steady-state  
406 pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for  
407 3 weeks.

408 *Warfarin:* In a study of 23 healthy volunteers, 3 weeks of treatment with AVODART  
409 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or  
410 alter the effect of warfarin on prothrombin time when administered with warfarin.

411 *Other Concomitant Therapy:* Although specific interaction studies were not  
412 performed with other compounds, approximately 90% of the subjects in the 3 Phase 3 pivotal  
413 efficacy studies receiving AVODART were taking other medications concomitantly. No

414 clinically significant adverse interactions could be attributed to the combination of AVODART  
415 and concurrent therapy when AVODART was coadministered with anti-hyperlipidemics,  
416 angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium  
417 channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs),  
418 phosphodiesterase Type V inhibitors, and quinolone antibiotics.

## 419 **13 NONCLINICAL TOXICOLOGY**

### 420 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

427 In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and  
428 53 mg/kg/day for males and 0.8, 6.3, and 15 mg/kg/day for females, there was an increase in  
429 Leydig cell adenomas in the testes at 53 mg/kg/day (135-fold the expected clinical exposure). An  
430 increased incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/day (52-fold the  
431 expected clinical exposure) and 53 mg/kg/day in male rats. A positive correlation between  
432 proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels  
433 has been demonstrated with 5 $\alpha$ -reductase inhibitors and is consistent with an effect on the  
434 hypothalamic-pituitary-testicular axis following 5 $\alpha$ -reductase inhibition. At tumorigenic doses in  
435 rats, luteinizing hormone levels in rats were increased by 167%. In this study, the major human  
436 metabolites were tested for carcinogenicity at approximately 1 to 3 times the expected clinical  
437 exposure.

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

442 Impairment of Fertility: Treatment of sexually mature male rats with dutasteride at doses  
443 of 0.05, 10, 50, and 500 mg/kg/day (0.1- to 110-fold the expected clinical exposure of parent  
444 drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility; reduced  
445 cauda epididymal (absolute) sperm counts but not sperm concentration (at 50 and  
446 500 mg/kg/day); reduced weights of the epididymis, prostate, and seminal vesicles; and  
447 microscopic changes in the male reproductive organs. The fertility effects were reversed by  
448 recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery  
449 period. The 5 $\alpha$ -reductase-related changes consisted of cytoplasmic vacuolation of tubular  
450 epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with  
451 decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were  
452 no longer present at recovery week 14 in the low-dose group and were partly recovered in the

453 remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/mL) were detected in the  
454 serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/day for 29 to  
455 30 weeks.

456 In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5,  
457 12.5, and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption and  
458 feminization of male fetuses (decreased anogenital distance) at doses of  $\geq 2.5$  mg/kg/day (2- to  
459 10-fold the clinical exposure of parent drug in men). Fetal body weights were also reduced at  
460  $\geq 0.05$  mg/kg/day in rats ( $< 0.02$ -fold the human exposure).

### 461 **13.2 Animal Toxicology**

462 Central Nervous System Toxicology Studies: In rats and dogs, repeated oral  
463 administration of dutasteride resulted in some animals showing signs of non-specific, reversible,  
464 centrally-mediated toxicity without associated histopathological changes at exposure 425- and  
465 315-fold the expected clinical exposure (of parent drug), respectively.

### 466 **13.3 Reproductive and Developmental Toxicity**

467 In an intravenous embryo-fetal development study in the rhesus monkey (12/group),  
468 administration of dutasteride at 400, 780, 1,325, or 2,010 ng/day on gestation days 20 to 100 did  
469 not adversely affect development of male external genitalia. Reduction of fetal adrenal weights,  
470 reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were  
471 observed in monkeys treated with the highest dose. Based on the highest measured semen  
472 concentration of dutasteride in treated men (14 ng/mL), these doses represent 0.8 to 16 times  
473 based on blood levels of parent drug (32 to 186 times based on a ng/kg daily dose) the potential  
474 maximum exposure of a 50-kg human female to 5 mL semen daily from a dutasteride-treated  
475 man, assuming 100% absorption. Dutasteride is highly bound to proteins in human semen  
476 ( $> 96\%$ ), potentially reducing the amount of dutasteride available for vaginal absorption.

477 In an embryo-fetal development study in female rats, oral administration of dutasteride at  
478 doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in feminization of male fetuses (decreased  
479 anogenital distance) and male offspring (nipple development, hypospadias, and distended  
480 preputial glands) at all doses (0.07- to 111-fold the expected male clinical exposure). An increase  
481 in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was observed at  
482 doses  $\geq 2.5$  mg/kg/day (15- to 111-fold the expected clinical exposure). Increased incidences of  
483 skeletal variations considered to be delays in ossification associated with reduced body weight  
484 were observed at doses of 12.5 and 30 mg/kg/day (56- to 111-fold the expected clinical  
485 exposure).

486 In an oral pre- and post-natal development study in rats, dutasteride doses of 0.05, 2.5,  
487 12.5, or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia  
488 (i.e., decreased anogenital distance, increased incidence of hypospadias, nipple development) of  
489 F1 generation male offspring occurred at doses  $\geq 2.5$  mg/kg/day (14- to 90-fold the expected  
490 clinical exposure in men). At a daily dose of 0.05 mg/kg/day (0.05-fold the expected clinical  
491 exposure), evidence of feminization was limited to a small, but statistically significant, decrease  
492 in anogenital distance. Doses of 2.5 to 30 mg/kg/day resulted in prolonged gestation in the



493 parental females and a decrease in time to vaginal patency for female offspring and a decrease in  
494 prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were  
495 noted at doses greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at  
496 30 mg/kg/day.

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

## 505 **14 CLINICAL STUDIES**

### 506 **14.1 Monotherapy**

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

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

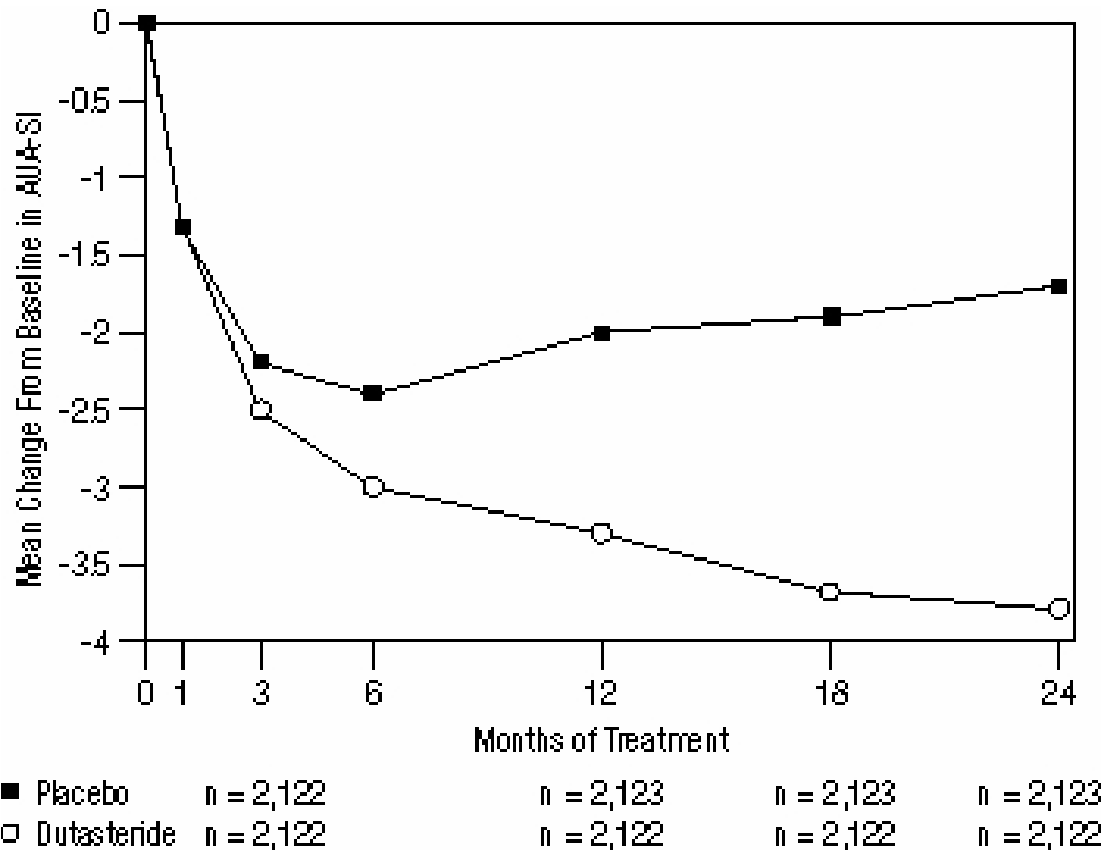
522 Subjects receiving dutasteride achieved statistically significant improvement in  
523 symptoms versus placebo by Month 3 in 1 study and by Month 12 in the other 2 pivotal studies.  
524 At Month 12, the mean decrease from baseline in AUA-SI symptom scores across the 3 studies  
525 pooled was -3.3 units for dutasteride and -2.0 units for placebo with a mean difference between  
526 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  
527 consistent across the 3 studies. At Month 24, the mean decrease from baseline was  
528 -3.8 units for dutasteride and -1.7 units for placebo with a mean difference of -2.1 (range, -1.9 to  
529 -2.2 units in each of the 3 studies,  $p < 0.001$ ). See Figure 1. The improvement in BPH symptoms  
530 seen during the first 2 years of double-blind treatment was maintained throughout an additional  
531 2 years of open-label extension studies.

532 These studies were prospectively designed to evaluate effects on symptoms based on  
 533 prostate size at baseline. In men with prostate volumes  $\geq 40$  cc, the mean decrease was -3.8 units  
 534 for dutasteride and -1.6 units for placebo, with a mean difference between the 2 treatment groups  
 535 of -2.2 at Month 24. In men with prostate volumes  $< 40$  cc, the mean decrease was -3.7 units for  
 536 dutasteride and -2.2 units for placebo, with a mean difference between the 2 treatment groups of  
 537 -1.5 at Month 24.

538

539 **Figure 1. AUA-SI Score\* Change from Baseline (Randomized, Double-Blind,**  
 540 **Placebo-Controlled Studies Pooled)**

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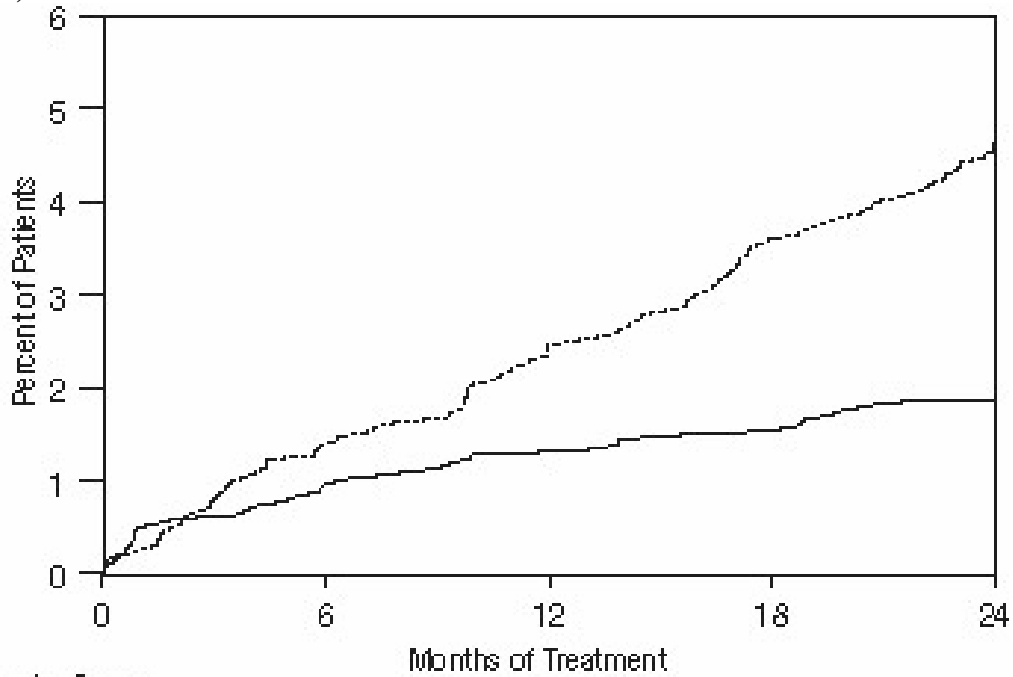
543 \*AUA-SI score ranges from 0 to 35.

544

545 Effect on Acute Urinary Retention and the Need for Surgery: Efficacy was also  
 546 assessed after 2 years of treatment by the incidence of AUR requiring catheterization and  
 547 BPH-related urological surgical intervention. Compared with placebo, AVODART was  
 548 associated with a statistically significantly lower incidence of AUR (1.8% for AVODART vs.  
 549 4.2% for placebo,  $p < 0.001$ ; 57% reduction in risk, [95% CI: 38% to 71%]) and with a  
 550 statistically significantly lower incidence of surgery (2.2% for AVODART vs. 4.1% for placebo,  
 551  $p < 0.001$ ; 48% reduction in risk, [95% CI: 26% to 63%]). See Figures 2 and 3.

552

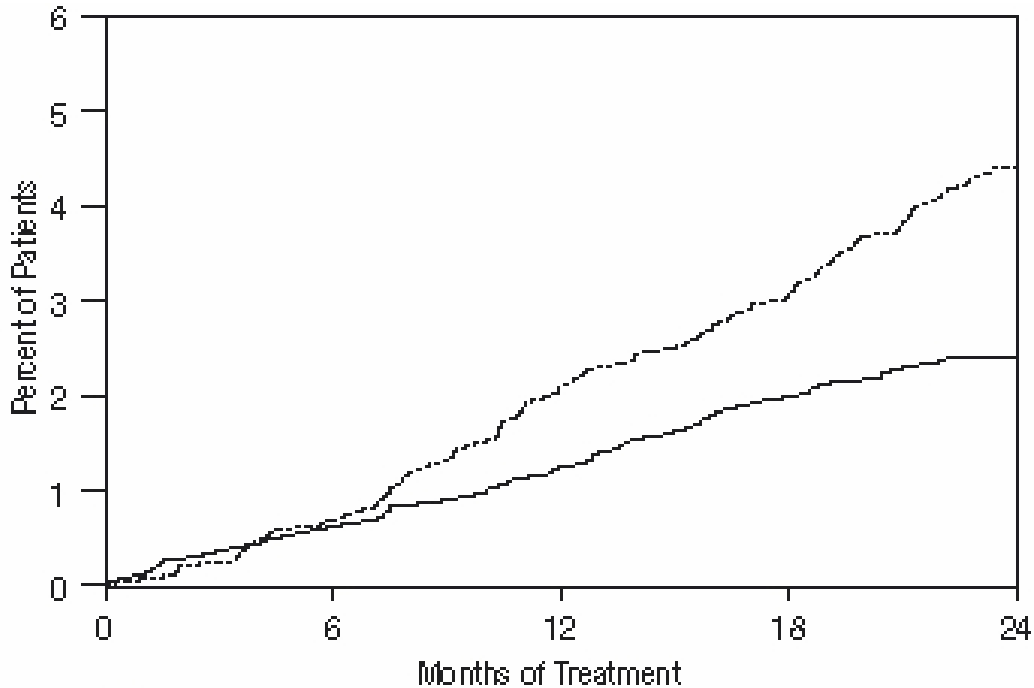
553 **Figure 2. Percent of Subjects Developing Acute Urinary Retention Over a**  
 554 **24-Month Period (Randomized, Double-Blind, Placebo-Controlled Studies**  
 555 **Pooled)**



	0	6	12	18	24
--- Placebo Group					
No. of events, cumulative	0	28	49	70	90
No. at risk	2,158	2,158	2,038	1,919	1,793
— Dutasteride Group					
No. of events, cumulative	0	19	27	31	39
No. at risk	2,167	2,167	2,052	1,928	1,827

556  
557

558 **Figure 3. Percent of Subjects Having Surgery for Benign Prostatic Hyperplasia**  
 559 **Over a 24-Month Period (Randomized, Double-Blind, Placebo-Controlled**  
 560 **Studies Pooled)**  
 561



--- 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

562  
 563

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

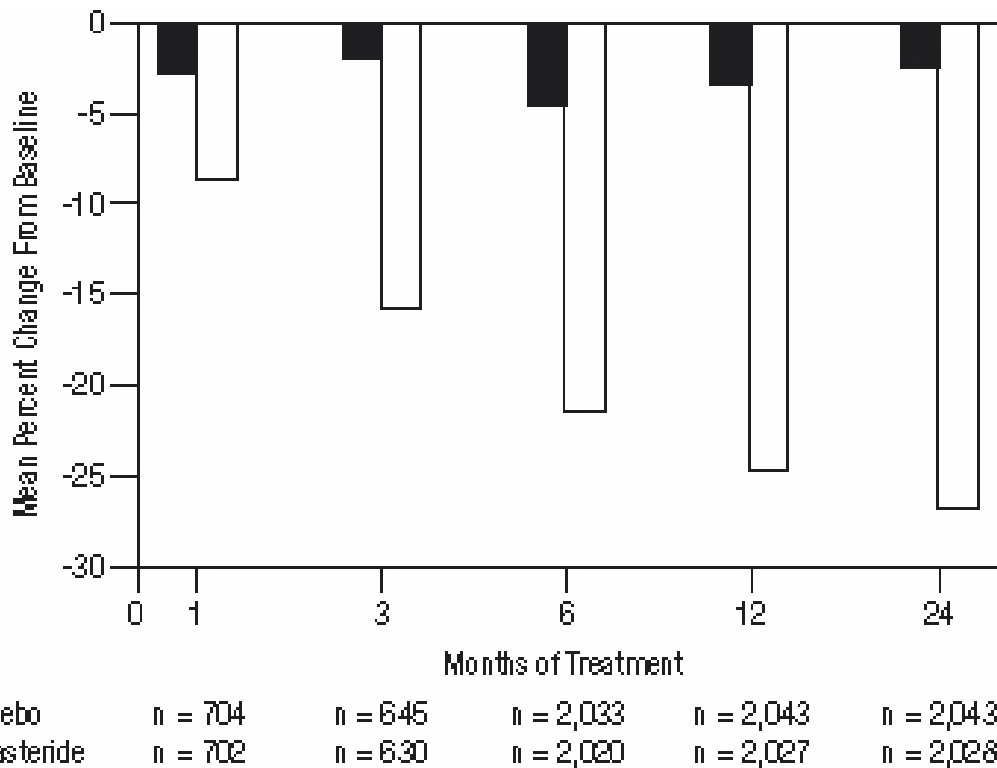
567 Statistically significant differences (AVODART versus placebo) were noted at the  
 568 earliest post-treatment prostate volume measurement in each study (Month 1, Month 3, or  
 569 Month 6) and continued through Month 24. At Month 12, the mean percent change in prostate  
 570 volume across the 3 studies pooled was -24.7% for dutasteride and -3.4% for placebo; the mean  
 571 difference (dutasteride minus placebo) was -21.3% (range, -21.0% to -21.6% in each of the  
 572 3 studies,  $p < 0.001$ ). At Month 24, the mean percent change in prostate volume across the  
 573 3 studies pooled was -26.7% for dutasteride and -2.2% for placebo with a mean difference of  
 574 -24.5% (range, -24.0% to -25.1% in each of the 3 studies,  $p < 0.001$ ). See Figure 4. The reduction  
 575 in prostate volume seen during the first 2 years of double-blind treatment was maintained

576 throughout an additional 2 years of open-label extension studies.

577

578 **Figure 4. Prostate Volume Percent Change from Baseline (Randomized, Double-Blind,**  
579 **Placebo-Controlled Studies Pooled)**

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581

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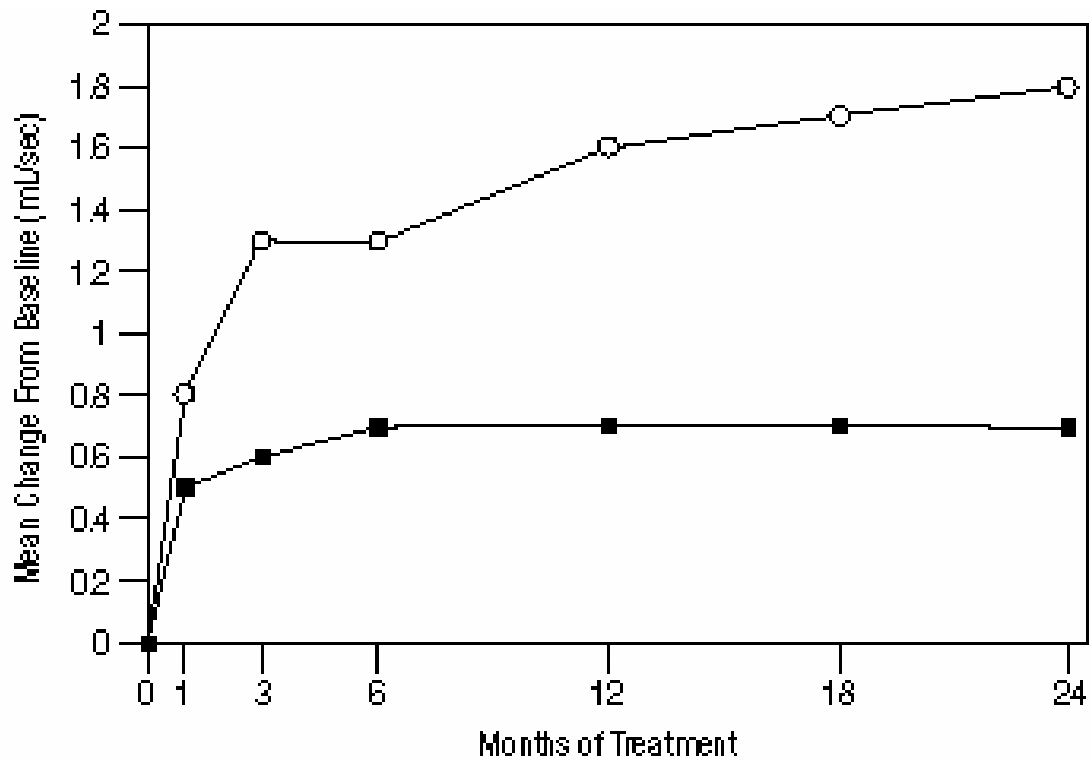
583 Effect on Maximum Urine Flow Rate: A mean peak urine flow rate ( $Q_{max}$ ) of  
584  $\leq 15$  mL/sec was required for study entry.  $Q_{max}$  was approximately 10 mL/sec at baseline across  
585 the 3 pivotal studies.

586 Differences between the 2 groups were statistically significant from baseline at Month 3  
587 in all 3 studies and were maintained through Month 12. At Month 12, the mean increase in  $Q_{max}$   
588 across the 3 studies pooled was 1.6 mL/sec for AVODART and 0.7 mL/sec for placebo; the  
589 mean difference (dutasteride minus placebo) was 0.8 mL/sec (range, 0.7 to 1.0 mL/sec in each of  
590 the 3 studies,  $p < 0.001$ ). At Month 24, the mean increase in  $Q_{max}$  was 1.8 mL/sec for dutasteride  
591 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  
592 each of the 3 studies,  $p < 0.001$ ). See Figure 5. The increase in maximum urine flow rate seen  
593 during the first 2 years of double-blind treatment was maintained throughout an additional  
594 2 years of open-label extension studies.

595

596 **Figure 5. Q<sub>max</sub> Change from Baseline (Randomized, Double-Blind, Placebo-Controlled**  
 597 **Studies Pooled)**

598



■ 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

599  
600

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

606 **14.2 Combination With Alpha-Blocker Therapy (CombAT)**

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The efficacy of combination therapy (AVODART 0.5 mg/day plus tamsulosin 0.4 mg/day, n = 1,610) was compared with AVODART alone (n = 1,623) or tamsulosin alone (n = 1,611) in a 4-year multicenter, randomized, double-blind study. Study entry criteria were similar to the Phase 3 monotherapy efficacy trials described above in section 14.1. The results presented below are from data collected following 2 years of treatment in the 4-year study. Eighty-eight percent (88%) of the enrolled study population was Caucasian. Approximately 52% of subjects had previous exposure to 5 $\alpha$ -reductase inhibitor or alpha-blocker treatment. The primary efficacy endpoint evaluated during the first 2 years of treatment was change in international prostate symptom score (IPSS). Most of the 4,844 subjects randomly assigned to receive combination, AVODART, or tamsulosin completed 2 years of double-blind treatment

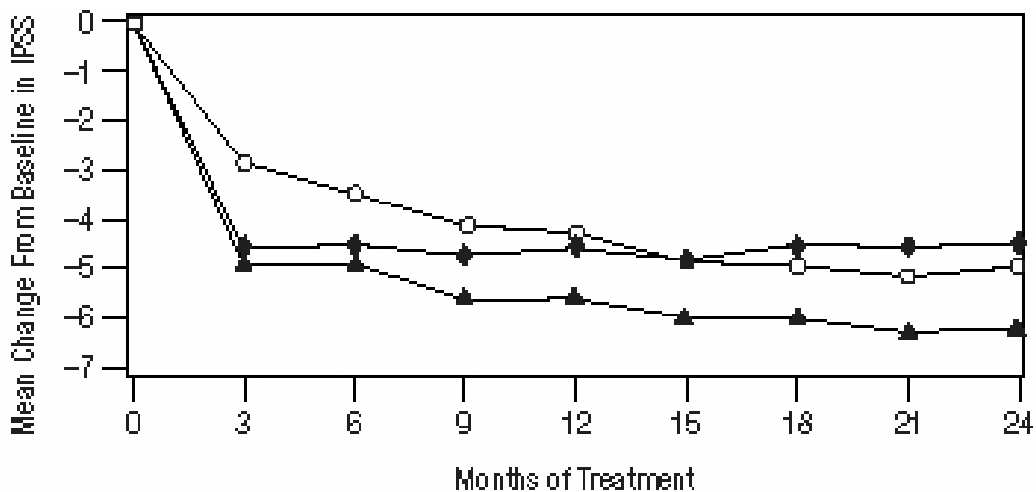
617 (79%, 80%, and 78%, respectively).

618 **Effect on Symptom Score:** Symptoms were quantified using the first 7 questions of the  
 619 IPSS (identical to the AUA-SI). The baseline score was approximately 16.4 units for each  
 620 treatment group. Combination therapy was statistically superior to each of the monotherapy  
 621 treatments in decreasing symptom score at Month 24. This difference was seen by Month 9 and  
 622 continued through Month 24. At Month 24, the mean change from baseline ( $\pm$ SD) in IPSS  
 623 symptom scores was -6.2 ( $\pm$ 7.14) for combination, -4.9 ( $\pm$ 6.81) for AVODART, and -4.3 ( $\pm$ 7.01)  
 624 for tamsulosin, with a mean difference between combination and AVODART of -1.3 units  
 625 ( $p < 0.001$ ; [95% CI: -1.69, -0.86]), and between combination and tamsulosin of -1.8 units  
 626 ( $p < 0.001$ ; [95% CI: -2.23, -1.40]). See Figure 6.

627

628 **Figure 6. International Prostate Symptom Score Change from Baseline (CombAT study)**

629



▲ Dutasteride+tamsulosin	n= 1,584	n= 1,572	n= 1,575	n= 1,575	n= 1,575
□ Dutasteride 0.5 mg	n= 1,582	n= 1,591	n= 1,592	n= 1,592	n= 1,592
◆ Tamsulosin 0.4 mg	n= 1,573	n= 1,581	n= 1,582	n= 1,582	n= 1,582

630

631

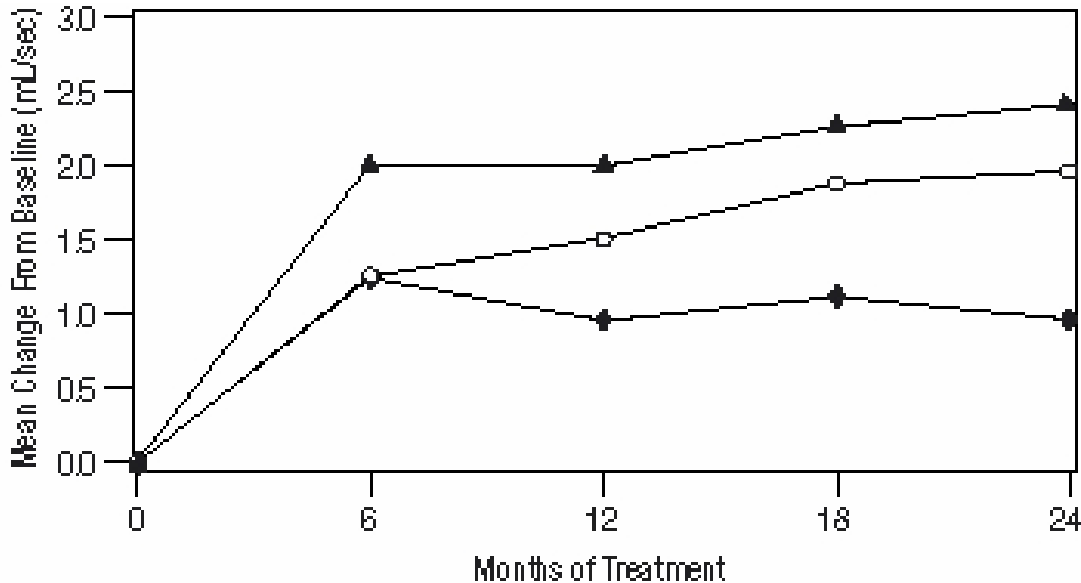
632 **Effect on Maximum Urine Flow Rate:** The baseline  $Q_{max}$  was approximately  
 633 10.7 mL/sec for each treatment group. Combination therapy was statistically superior to each of  
 634 the monotherapy treatments in increasing  $Q_{max}$  at Month 24. This difference was seen by  
 635 Month 6 and continued through Month 24. At Month 24, the mean increase from baseline ( $\pm$ SD)  
 636 in  $Q_{max}$  was 2.4 ( $\pm$ 5.26) mL/sec for combination, 1.9 ( $\pm$ 5.10) mL/sec for AVODART, and  
 637 0.9 ( $\pm$ 4.57) mL/sec for tamsulosin, with a mean difference between combination and  
 638 AVODART of 0.5 mL/sec ( $p = 0.003$ ; [95% CI: 0.17, 0.84]), and between combination and  
 639 tamsulosin of 1.5 mL/sec ( $p < 0.001$ ; [95% CI: 1.19, 1.86]). See Figure 7.

640



641 **Figure 7. Q<sub>max</sub> Change from Baseline (CombAT study)**

642



▲ Dutasteride + tamsulosin	n = 1,388	n = 1,477	n = 1,487	n = 1,492
○ Dutasteride 0.5 mg	n = 1,406	n = 1,483	n = 1,496	n = 1,502
◆ Tamsulosin 0.4 mg	n = 1,445	n = 1,510	n = 1,517	n = 1,519

643

644

645 **Effect on Prostate Volume:** The mean prostate volume at study entry was  
 646 approximately 55 cc. At Month 24, the mean percent change from baseline ( $\pm$ SD) in prostate  
 647 volume was -26.9% ( $\pm$ 22.57) for combination therapy, -28.0% ( $\pm$ 24.88) for AVODART, and 0%  
 648 ( $\pm$ 31.14) for tamsulosin, with a mean difference between combination and AVODART of 1.1%  
 649 ( $p = \text{NS}$ ; [95% CI: -0.6, 2.8]), and between combination and tamsulosin of -26.9% ( $p < 0.001$ ;  
 650 [95% CI: -28.9, -24.9]).

651 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

657 Dutasteride is absorbed through the skin. AVODART Capsules should not be handled by  
 658 women who are pregnant or who may become pregnant because of the potential for absorption of  
 659 dutasteride and the subsequent potential risk to a developing male fetus [see *Warnings and*  
 660 *Precautions (5.1)*].

661 **17 PATIENT COUNSELING INFORMATION**

662 See FDA-Approved Patient Labeling

663 **17.1 Exposure of Women—Risk to Male Fetus**

664 Physicians should inform patients that AVODART Capsules should not be handled by a  
665 woman who is pregnant or who may become pregnant because of the potential for absorption of  
666 dutasteride and the subsequent potential risk to a developing male fetus. Dutasteride is absorbed  
667 through the skin and could result in unintended fetal exposure. If a pregnant woman or woman of  
668 childbearing potential comes in contact with leaking AVODART Capsules, the contact area  
669 should be washed immediately with soap and water [*see Warnings and Precautions (5.1),*  
670 *Specific Populations (8.1)*].

671 **17.2 Blood Donation**

672 Physicians should inform men treated with AVODART that they should not donate blood  
673 until at least 6 months following their last dose to prevent pregnant women from receiving  
674 dutasteride through blood transfusion [*see Warnings and Precautions (5.4)*]. Serum levels of  
675 dutasteride are detectable for 4 to 6 months after treatment ends [*see Clinical Pharmacology*  
676 *(12.3)*].

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683 Manufactured by Cardinal Health, Beinheim, France for  
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## **Patient Information**

### **AVODART® (dutasteride) Soft Gelatin Capsules**

#### **AVODART is for use by men only.**

Read this information carefully before you start taking AVODART. Read the information you get with AVODART each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

#### **What is AVODART?**

AVODART is a medication for the treatment of symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

- 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

AVODART is not a treatment for prostate cancer. See the end of this leaflet for information about how AVODART works.

#### **Who should NOT take AVODART?**

- Women and children should not take AVODART. A woman who is pregnant or capable of becoming pregnant should not handle AVODART capsules. See **“What are the special warnings for women about AVODART?”**
- Do not take AVODART if you have had an allergic reaction to AVODART or any of its ingredients.

#### **What are the special warnings for women about AVODART?**

- Women should never take AVODART.
- Women who are pregnant or may become pregnant should not handle AVODART Capsules. If a woman who is pregnant with a male baby gets enough AVODART into her body after swallowing it or through her skin after handling it, the male baby may be born with abnormal sex organs.

#### **What are the special precautions about AVODART?**

- Men treated with AVODART should not donate blood until at least 6 months after their final dose to prevent giving AVODART to a pregnant female through a blood transfusion.
- Tell your doctor if you have liver problems. AVODART may not be right for you.

#### **How should I take AVODART?**

- Take 1 AVODART capsule once a day.
- Swallow the capsule whole because the contents of the capsule may irritate your lips, mouth, or throat.
- You can take AVODART with or without food.

- If you miss a dose, you may take it later that day. Do not make up the missed dose by taking 2 doses the next day.
- You may find it helpful to take AVODART at the same time every day to help you remember to take your dose.

### **What are the possible side effects of AVODART?**

Possible side effects are impotence (trouble getting or keeping an erection), a decrease in libido (sex drive), enlarged breasts, a decrease in the amount of semen released during sex, and allergic reactions such as rash, itching, hives, and swelling of the lips or face. These events occurred infrequently.

Talk with your doctor if you have questions about these and other side effects that you think may be related to taking AVODART.

### **How should I store AVODART?**

AVODART is a soft gelatin capsule that may become soft and leak or may stick to other capsules if kept at high temperatures. Store AVODART capsules at room temperature of 77°F (25°C) or lower.

If your capsules are cracked or leaking, don't use them, and contact your pharmacist.

### **General information about AVODART.**

- Do not use AVODART for a condition for which it was not prescribed.
- Do not share your AVODART.
- Ask your doctor about how often you should return for a visit to check your BPH.
- A blood test called PSA (prostate-specific antigen) is sometimes used to detect prostate cancer. AVODART will reduce the amount of PSA measured in your blood. Your doctor is aware of this effect and can still use PSA to detect prostate cancer in you.
- If you have questions about AVODART, ask your doctor or pharmacist. They can show you detailed information about AVODART that was written for healthcare professionals.

### **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. Just as your prostate became large over a long period of time, reducing the size of your prostate and improving your symptoms will take time. While some men have fewer problems and symptoms after 3 months of treatment with AVODART, a treatment period of at least 6 months is usually necessary to see if AVODART will work for you. Studies have shown that treatment with AVODART for 2 years reduces the risk of complete blockage of urine flow (acute urinary retention) and/or the need for surgery for benign prostatic hyperplasia.



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