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 5α-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 5α-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 ≥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: 6/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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 5α-reductase, which prevents conversion of testosterone to dihydrotesterone, 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 5α-reductase inhibitors.

5 WARNINGS AND PRECAUTIONS

5.1 Exposure of Women—Risk to Male Fetus

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

5.2 Evaluation for Other Urological Diseases

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

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

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

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

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

5.4 Blood Donation

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

5.5 Effect on Semen Characteristics

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

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Monotherapy:

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

Over 4,300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg daily doses of AVODART in 3 identical 2-year, placebo-controlled, double-blind, Phase 3 treatment studies, each with 2-year open-label extensions. 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% 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 Reactions	Adverse Reaction Time of Onset			
	Month 0-6	Month 7-12	Month 13-18	Month 19-24
AVODART (n)	(n = 2,167)	(n = 1,901)	(n = 1,725)	(n = 1,605)
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*				
AVODART	0.5%	0.8%	1.1%	0.6%
Placebo	0.2%	0.3%	0.3%	0.1%

*Includes breast tenderness and breast enlargement.

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

Combination with Alpha-Blocker Therapy (CombAT):

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

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

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

Table 2. Adverse Reactions Reported Over a 24-Month Period in ≥1% of Subjects in Any Treatment Group (CombAT) by Time of Onset

Adverse Reactions	Adverse Reaction Time of Onset			
	Month 0-6	Month 7-12	Month 13-18	Month 19-24
Combination (n)*	(n = 1,610)	(n = 1,524)	(n = 1,424)	(n = 1,345)
AVODART (n)	(n = 1,623)	(n = 1,547)	(n = 1,457)	(n = 1,378)
Tamsulosin(n)	(n = 1,611)	(n = 1,542)	(n = 1,468)	(n = 1,363)
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†				
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%

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

†Includes breast tenderness and breast enlargement.

6.2 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

7.1 Cytochrome P450 3A Inhibitors

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

7.2 Alpha-Adrenergic Blocking Agents

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

7.3 Calcium Channel Antagonists

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

7.4 Cholestyramine

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

7.5 Digoxin

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

7.6 Warfarin

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X. *[See Contraindications (4)]*. AVODART is contraindicated for use in women of childbearing potential and during pregnancy. AVODART is a 5α-reductase inhibitor that prevents conversion of testosterone to dihydrotesterone (DHT), a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited normal development of external genitalia in male fetuses. 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.

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

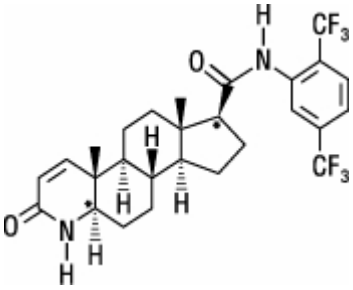
In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In a clinical study, daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for 6 months with no additional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

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

11 DESCRIPTION

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

Dutasteride is chemically designated as (5α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5 with the following structural formula:



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

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

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

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

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

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

12.3 Pharmacokinetics

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

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

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

11.5% of serum dutasteride concentrations partitioned into semen.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

13.2 Animal Toxicology

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

13.3 Reproductive and Developmental Toxicity

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

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

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

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

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

14 CLINICAL STUDIES

14.1 Monotherapy

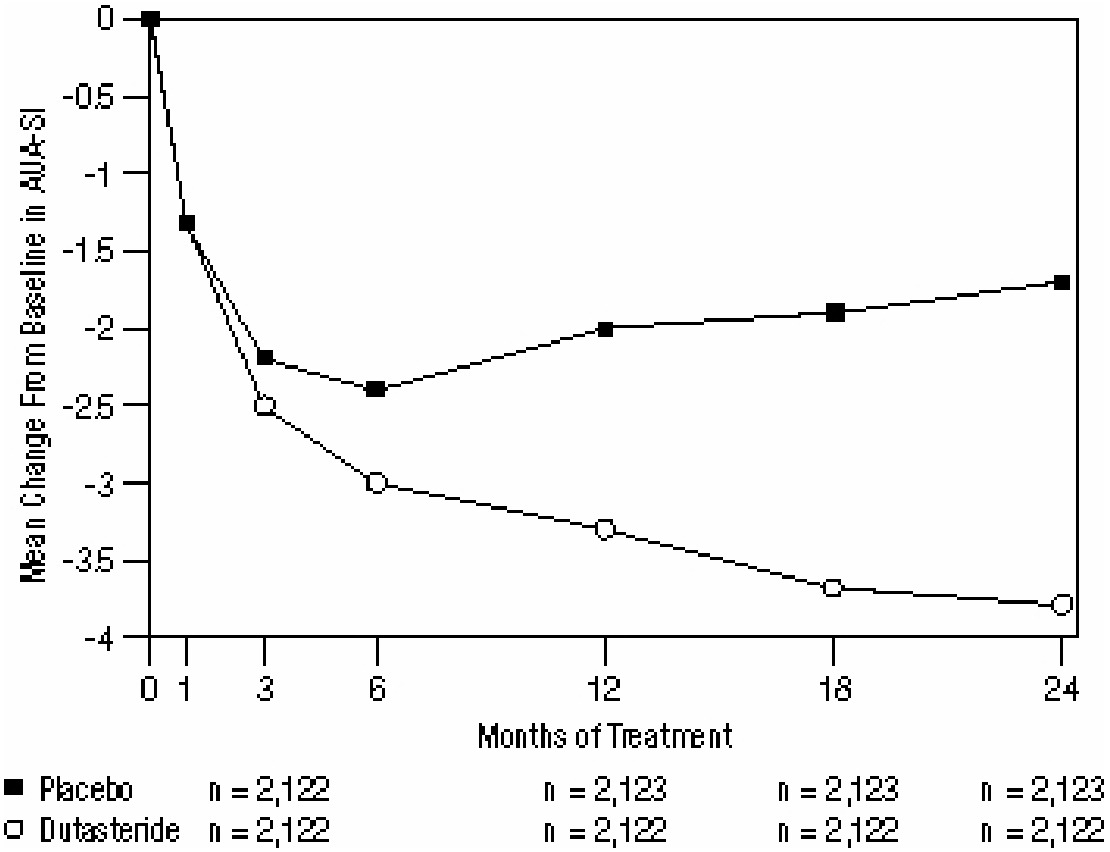
AVODART 0.5 mg/day (n = 2,167) or placebo (n = 2,158) was evaluated in male subjects with BPH in three 2-year multicenter, placebo-controlled, double-blind studies, each with 2-year open-label extensions (n = 2,340). More than 90% of the study population was Caucasian. Subjects were at least 50 years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

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

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

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

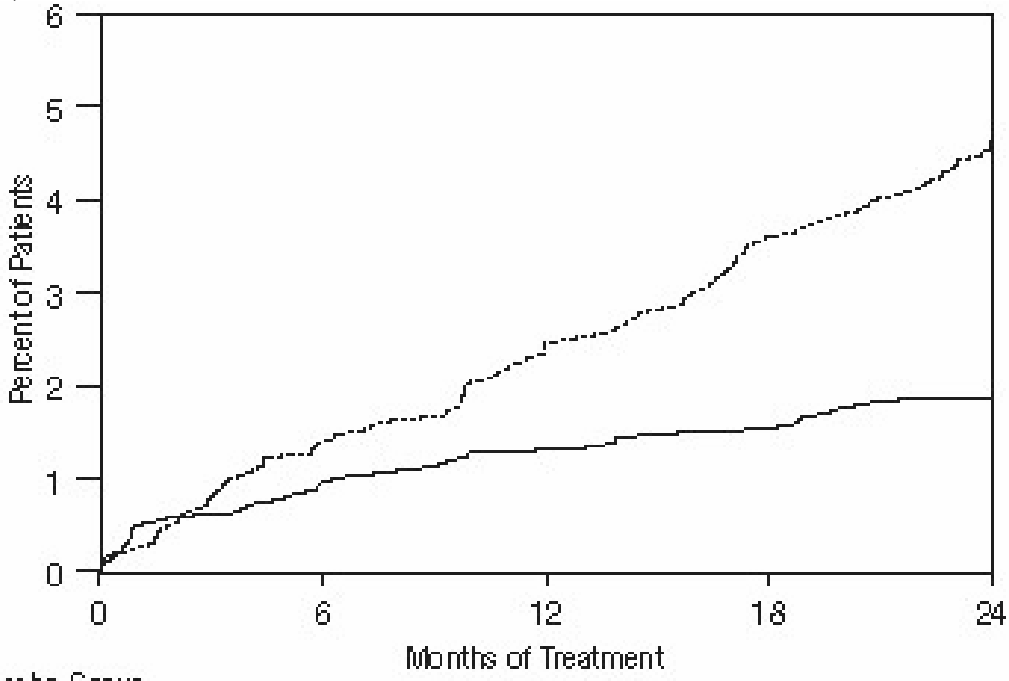
Figure 1. AUA-SI Score* Change from Baseline (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



*AUA-SI score ranges from 0 to 35.

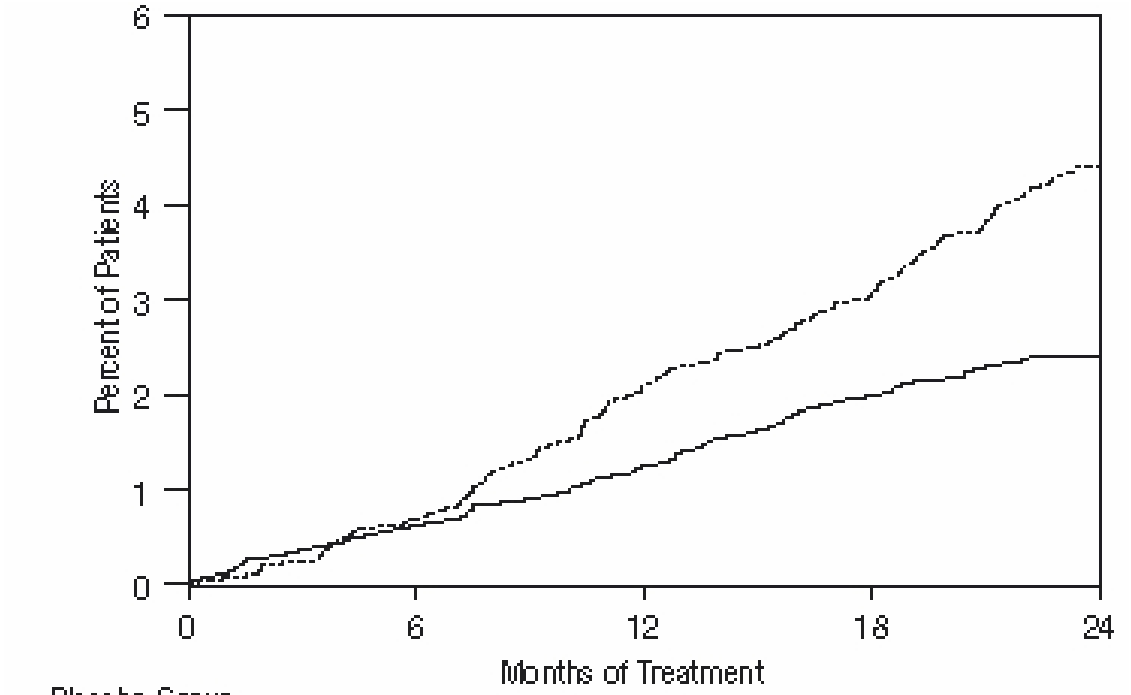
Effect on Acute Urinary Retention and the Need for Surgery: Efficacy was also assessed after 2 years of treatment by the incidence of AUR requiring catheterization and BPH-related urological surgical intervention. Compared with placebo, AVODART was associated with a statistically significantly lower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

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



---- Placebo Group				
No. of events, cumulative	28	49	70	90
No. at risk	2,158	2,039	1,919	1,793
— Dutasteride Group				
No. of events, cumulative	19	27	31	39
No. at risk	2,167	2,052	1,928	1,827

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



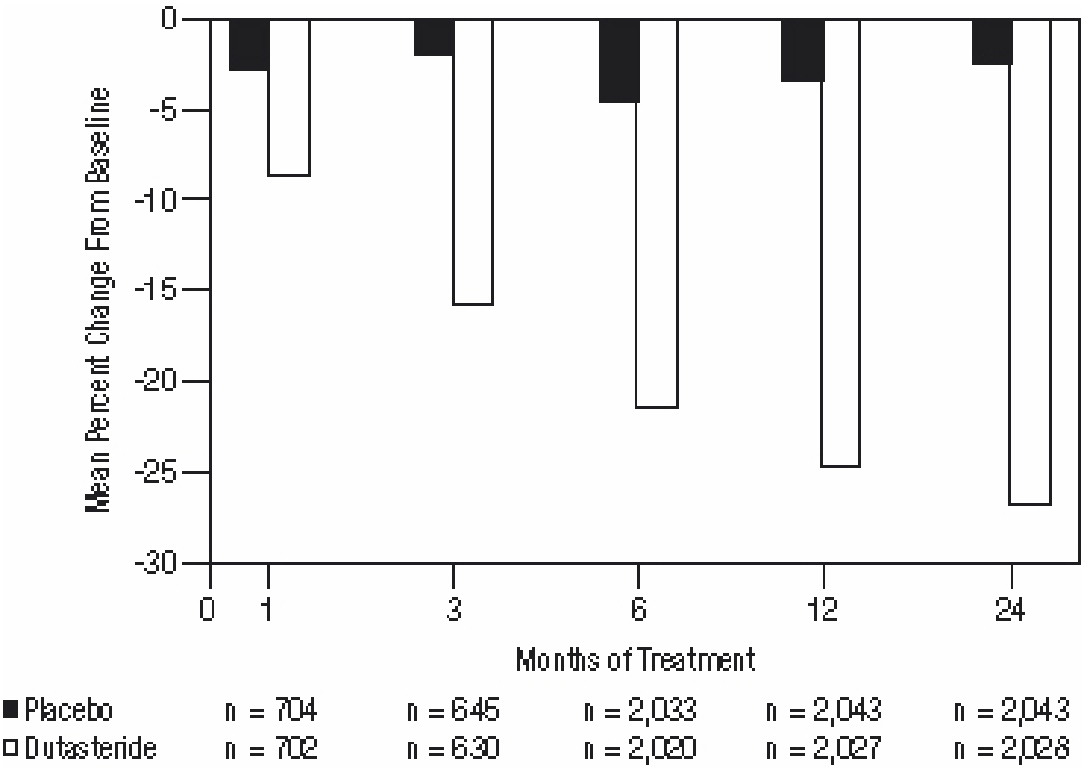
---- Placebo Group				
No. of events, cumulative	13	40	59	89
No. at risk	2,158	2,057	1,944	1,823
— Dutasteride Group				
No. of events, cumulative	12	25	39	47
No. at risk	2,167	2,064	1,944	1,846

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

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

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

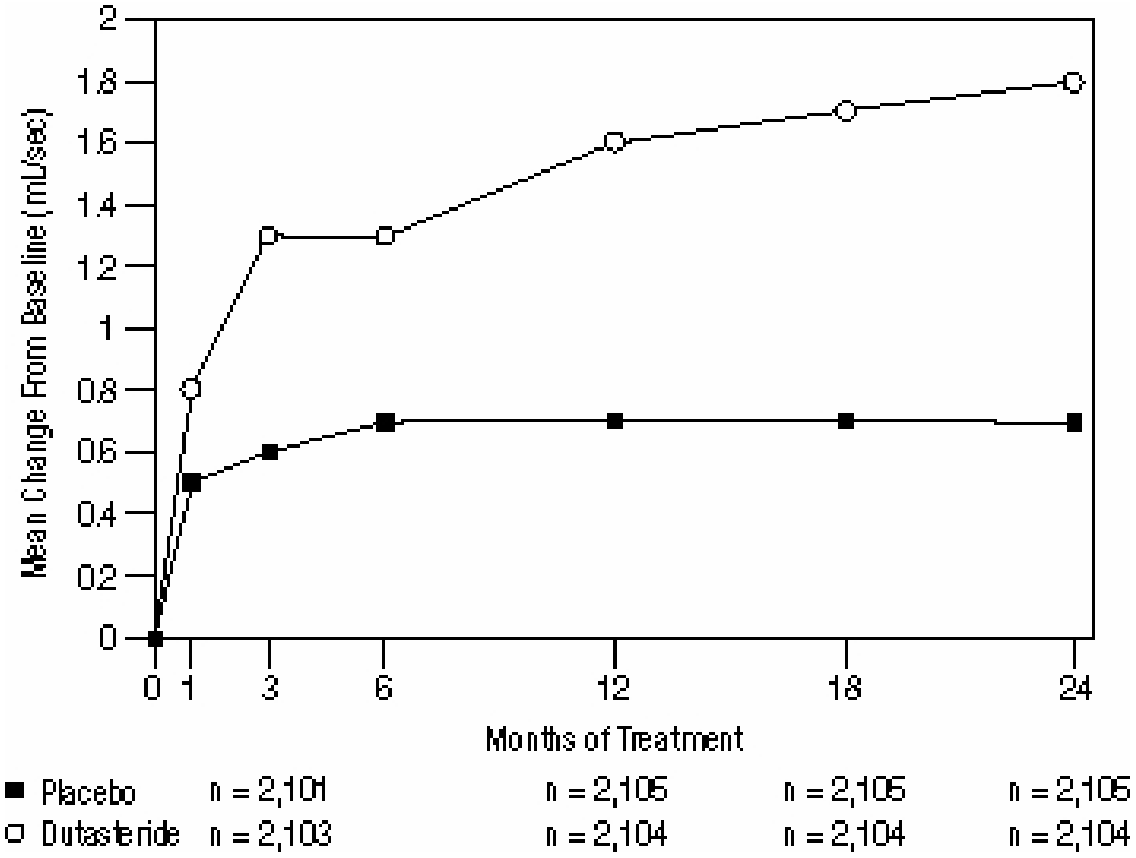
Figure 4. Prostate Volume Percent Change from Baseline (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



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

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

Figure 5. Q_{max} Change from Baseline (Randomized, Double-Blind, Placebo-Controlled Studies Pooled)



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

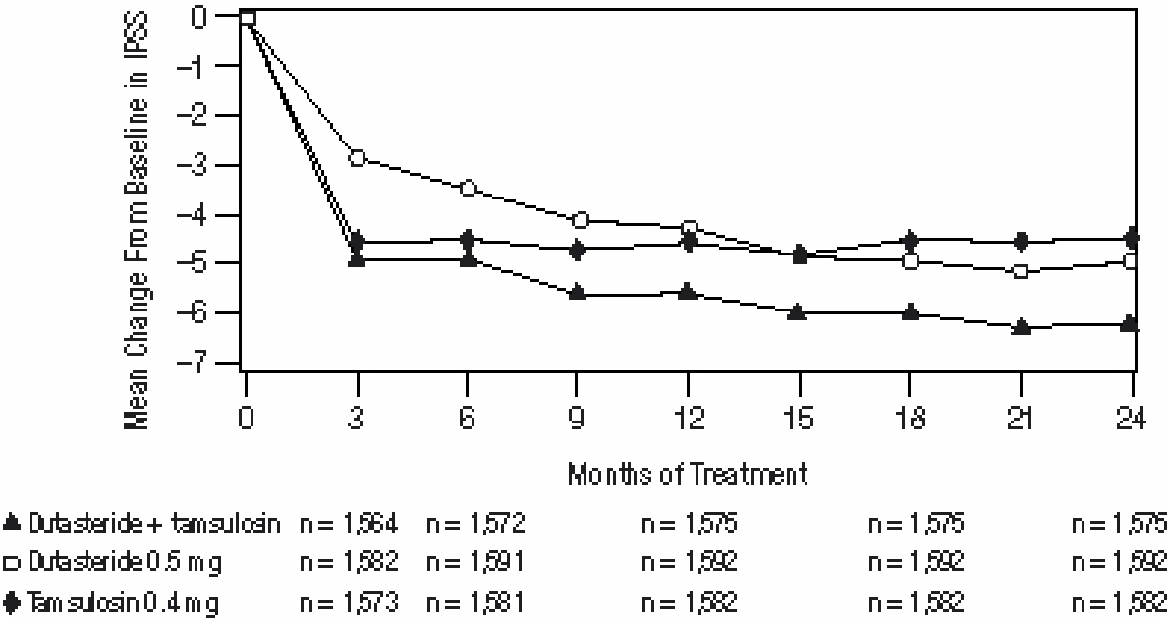
14.2 Combination With Alpha-Blocker Therapy (CombAT)

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 5α-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

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

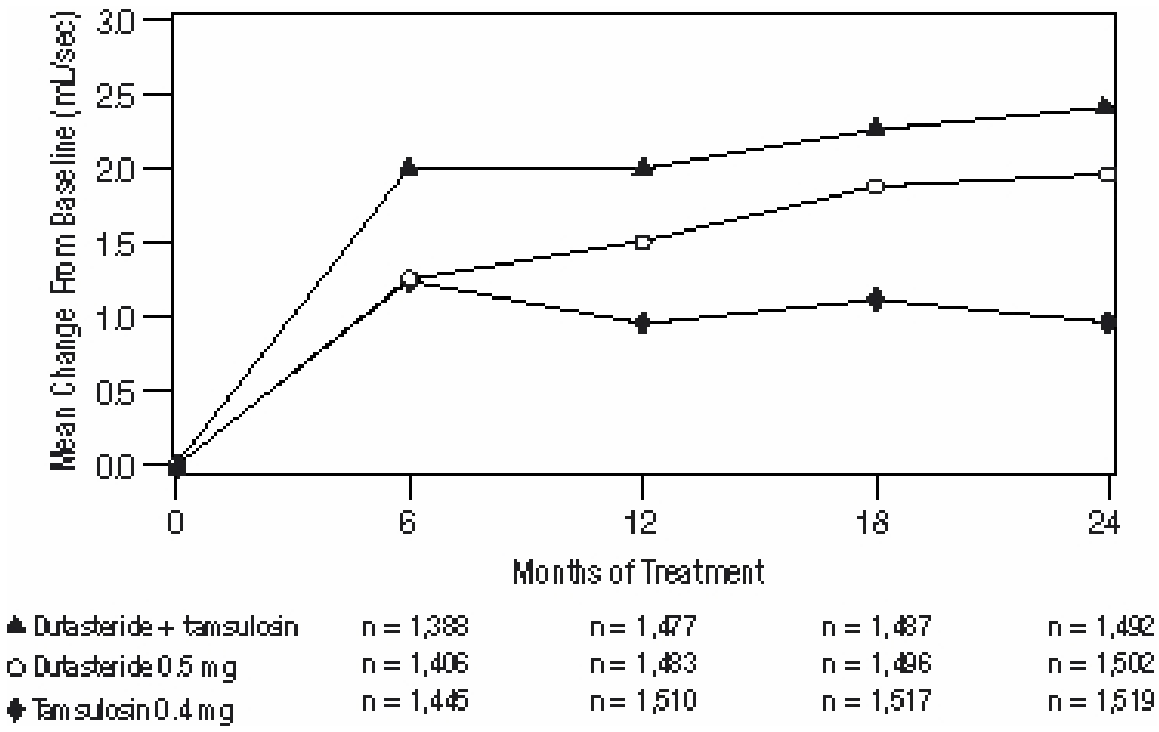
Effect on Symptom Score: Symptoms were quantified using the first 7 questions of the IPSS (identical to the AUA-SI). The baseline score was approximately 16.4 units for each treatment group. Combination therapy was statistically superior to each of the monotherapy treatments in decreasing symptom score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

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



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

Figure 7. Q_{max} Change from Baseline (CombAT study)



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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

17.1 Exposure of Women—Risk to Male Fetus

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

17.2 Blood Donation

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

GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured by Cardinal Health, Beinheim, France for
GlaxoSmithKline, Research Triangle Park, NC 27709

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.

Manufactured by Catalent Pharma Solutions
Beinheim, France for
GlaxoSmithKline
Research Triangle Park, NC 27709

October 2007 AVT:1PIL