

# Dutasteride

## Avodart<sup>®</sup>

### Softgel Capsule

#### PRODUCT DESCRIPTION

Dutasteride (Avodart<sup>®</sup>) is available as dull yellow, opaque, oblong soft gelatin capsules containing a clear, colourless to slightly yellow liquid. Each capsule is marked with GX CE2 on one side with red ink and contains 500 mcg Dutasteride for oral use.

#### PHARMACOLOGIC PROPERTIES

##### Pharmacodynamics

Dutasteride is a dual inhibitor of 5 alpha-reductase. It inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.

##### Effects on DHT/Testosterone

The maximum effect of daily doses of Dutasteride (Avodart<sup>®</sup>) on the reduction on DHT is dose-dependent and is observed within 1 to 2 weeks. After 1 week and 2 weeks of daily dosing of Dutasteride (Avodart<sup>®</sup>) 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 0.5 mg of dutasteride daily, the median decrease in DHT was 94% at 1 year and 93% at 2 years and the median increase in serum testosterone was 19% at both 1 and 2 years. This is an expected consequence of 5 alpha-reductase inhibition and did not result in any known adverse events.

##### Pharmacokinetics

##### Absorption

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 0.5 mg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours.

Absolute bioavailability in man is approximately 60% relative to a 2 hour intravenous infusion. The bioavailability of dutasteride is not affected by food.

##### 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 proteins (>99.5%).

Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months. Steady state serum concentrations (C<sub>ss</sub>) of approximately 40 nanograms/mL are achieved after 6 months of dosing 0.5 mg once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at 6 months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 nanograms/mL (range 0.4 to 14 nanograms/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

##### Biotransformation

*In vitro*, dutasteride is metabolised by the human cytochrome P450 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolized by CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.

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 five human serum metabolites of dutasteride have been detected in rat serum, however the stereochemistry of the hydroxyl additions at the 6 and 15 positions in the human and rat metabolites is not known.

##### Elimination

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0.5 mg/day to steady state in humans, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites comprising 39%, 21%, 7%, and 7% each of drug-related material and 6 minor metabolites (less than 5% each).

Only trace amounts of unchanged dutasteride (less than 0.1% of the dose) are detected in human urine.

At therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks.

Serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

##### Linearity/non-linearity

Dutasteride pharmacokinetics can be described as first order absorption process and two parallel elimination pathways, one saturable (concentration-dependent) and one non-saturable (concentration-independent).

At low serum concentrations (less than 3 nanograms/mL), dutasteride is cleared rapidly by both the concentration-dependent and concentration-independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 days.

At serum concentrations, greater than 3 nanograms/mL, dutasteride is cleared slowly (0.35 to 0.58 L/h) primarily by linear, non-saturable elimination with terminal half-life of 3 to 5 weeks. At therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower clearance dominates and the total clearance is linear and concentration-independent.

##### Elderly

Dutasteride pharmacokinetics and pharmacodynamics were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. Exposure of dutasteride, represented by AUC and C<sub>max</sub> values, was not statistically different when comparing age groups. Half-life was not statistically different when comparing the 50 to 69 year old group to the greater than 70 years old group, which encompasses the age of most men with BPH. No differences in drug effect as measured by DHT reduction were observed between age groups. Results indicated that no dutasteride dose-adjustment based on age is necessary.

### **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 on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see *Warnings and Precautions*).

### **Clinical Studies**

#### **Dutasteride (Avodart®) monotherapy for BPH**

Dutasteride 0.5 mg/day or placebo was evaluated in 4325 male subjects with enlarged prostates (greater than 30 cc) in three primary efficacy 2-year multicenter, placebo-controlled, double-blind studies.

In men with BPH, Dutasteride (Avodart®) treats and prevents disease progression by reducing the risk of both acute urinary retention (AUR) and the need for surgical intervention (SI) and by providing statistically significant improvement of lower urinary tract symptoms (LUTS), maximum urinary flow rate (Qmax) and prostate volume relative to placebo. These improvements in LUTS, Qmax and prostate volume were seen through to 24 months, and LUTS and Qmax continued to improve for a further 2 years in open-label extension studies. In addition, reductions in prostate volume were sustained for a further 2 years in open-label extension studies.

#### **Dutasteride (Avodart®) and tamsulosin combination therapy for BPH**

Dutasteride (Avodart®) 0.5 mg/day, tamsulosin 0.4mg/day or the combination of Dutasteride (Avodart®) 0.5mg plus tamsulosin 0.4mg was evaluated in 4844 male subjects with enlarged prostates (greater than or equal to 30cc) in a multicenter, double blind, parallel group study over 4 years. The primary efficacy endpoint at 2 years of treatment was the level of improvement from baseline in the international prostate symptom score (IPSS).

After 2 years of treatment, combination therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of -6.2 units. The adjusted mean improvements in symptom scores observed with the individual therapies were -4.9 units for Dutasteride (Avodart®) and -4.3 units for tamsulosin. The adjusted mean improvement in flow rate from baseline was 2.4 ml/sec for the combination, 1.9 ml/sec for Dutasteride (Avodart®) and 0.9 ml/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for the combination, -1.7 for Dutasteride (Avodart®) and -1.5 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 2 years of treatment was statistically significant for combination therapy compared to tamsulosin monotherapy alone.

The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH-related surgery. After 4 years of treatment, combination therapy statistically significantly reduced the risk of AUR or BPH-related surgery (65.8% reduction in risk  $p < 0.001$  [95% CI 54.7% to 74.1%]) compared to tamsulosin monotherapy. The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 11.9% for tamsulosin ( $p < 0.001$ ). Compared to Dutasteride (Avodart®) monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6%; the difference between treatment groups was not significant ( $p = 0.18$  [95% CI -10.9% to 41.7%]). The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 5.2% for Dutasteride (Avodart®).

Clinical progression was defined as a composite of worsening symptoms, (IPSS), and BPH-related events of AUR, incontinence, UTI, and renal insufficiency. Combination therapy was associated with a statistically significantly lower rate of clinical progression compared with tamsulosin ( $p < 0.001$ , 44.1% risk reduction [95% CI: 33.6% to 53.0%]) after 4 years. The rates of clinical progression for combination therapy, tamsulosin, and Dutasteride (Avodart®) were: 12.6%, 21.5%, and 17.8%, respectively.

The statistically significant adjusted mean improvement in symptom scores (IPSS) from baseline was maintained from year 2 to year 4. At 4 years, the adjusted mean improvements in symptom scores observed were -6.3 units for combination therapy, -5.3 units for Dutasteride (Avodart®) monotherapy and -3.8 units for tamsulosin monotherapy.

After 4 years of treatment, the adjusted mean improvement in flow rate (Qmax) from baseline was 2.4 ml/sec for combination therapy, 2.0 ml/sec for Dutasteride (Avodart®) monotherapy and 0.7 ml/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Qmax was statistically significantly greater with combination therapy at each 6-month assessment from Month 6 to Month 48 ( $p < 0.001$ ). Compared with Dutasteride (Avodart®), the adjusted mean improvement from baseline in Qmax was not statistically significantly different than with combination therapy ( $p = 0.050$  at Month 48).

Combination therapy was significantly superior ( $p < 0.001$ ) to tamsulosin monotherapy and to Dutasteride (Avodart®) monotherapy for the improvement in health outcome parameters BII and BPH-related Health Status (BHS) at 4 years. The adjusted mean improvement in BII from baseline was -2.2 units for the combination, -1.8 for AVODART and -1.2 for tamsulosin. The adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 for Dutasteride (Avodart®) and -1.1 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 4 years of treatment was statistically significant for combination therapy compared to tamsulosin monotherapy alone.

#### **Cardiac Failure**

In a 4-year comparison of Dutasteride (Avodart®) coadministered with Tamsulosin and Dutasteride and Tamsulosin monotherapy in men with BPH (the CombAT study), the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: Dutasteride (Avodart®), 4/1623 (0.2%) and tamsulosin, 10/1611, (0.6%). The relative risk estimate for time to first cardiac failure event was 3.57 [95% CI 1.17, 10.8] for combination treatment compared to Dutasteride (Avodart®) monotherapy and 1.36 [95% CI 0.61, 3.07] compared to tamsulosin monotherapy. No causal relationship between Dutasteride (Avodart®) (alone or in combination with an alpha blocker) and cardiac failure has been established (see *Warnings and Precautions*).

In a 4-year comparison of placebo and Dutasteride (Avodart®) in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study) there was a higher incidence of the composite term cardiac failure in subjects taking Dutasteride (Avodart®) (30/4105, 0.7%) versus placebo (16/4126, 0.4%) for a relative risk estimate for time to first cardiac failure event of 1.91 [95% CI 1.04, 3.50]. In a post-hoc analysis of concomitant alpha blocker use, there was a higher incidence of the composite term cardiac failure in subjects taking Dutasteride (Avodart®) and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking Dutasteride

(Avodart<sup>®</sup>) and an alpha blocker concomitantly: Dutasteride (Avodart<sup>®</sup>) and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), placebo and no alpha blocker (15/2727, 0.6%). No causal relationship between Dutasteride (Avodart<sup>®</sup>) (alone or in combination with an alpha blocker) and cardiac failure has been established (see Warnings and Precautions).

#### **Prostate cancer and high grade tumours**

In a 4-year comparison of placebo and Dutasteride (Avodart<sup>®</sup>) in 8231 men aged 50-75, with a prior negative biopsy for prostate cancer and baseline PDSA between 2.5ng/mL and 10.0ng/mL (the REDUCE study), 6,706 subjects had prostate needle biopsy data available for analysis to determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6). There was no difference in the incidence of Gleason 7-10 cancers ( $p=0.81$ ).

There was a higher incidence of Gleason 8-10 prostate cancers in the Dutasteride (Avodart<sup>®</sup>) group ( $n=29$ , 0.9%) compared to the placebo group ( $n=19$ , 0.6%) ( $p=0.15$ ). In Years 1-2, the number of subjects with Gleason 8-10 cancers was similar in the Dutasteride (Avodart<sup>®</sup>) group ( $n=17$ , 0.5%) and the placebo group ( $n=18$ , 0.5%). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the Dutasteride (Avodart<sup>®</sup>) group ( $n=12$ , 0.5%) compared with the placebo group ( $n=1$ , <0.1%) ( $p=0.0035$ ). There are no data available on the effect of Dutasteride (Avodart<sup>®</sup>) beyond 4 years in men at risk of prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the Dutasteride (Avodart<sup>®</sup>) group (0.5% in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5%, respectively). In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were ( $n=8$ , 0.5%) for Dutasteride (Avodart<sup>®</sup>), ( $n=11$ , 0.7%) for Tamsulosin and ( $n=5$ , 0.3%) for combination therapy (see Warnings and Precautions).

#### **Effects on prostate specific antigen (PSA) and prostate cancer detection**

In a 4-year comparison of placebo and Dutasteride in 8231 men aged 50-75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5ng/mL and 10.0ng/mL (the REDUCE study), Dutasteride (Avodart<sup>®</sup>) treatment caused a decrease in mean serum PSA by approximately 50% after six months of treatment with a large variability (standard deviation of 30%) among patients. The PSA suppression observed at six months was similar in men who did or who did not develop biopsy-detectable prostate cancer during the study (see Warnings and Precautions).

#### **Incidence of breast cancer**

In BPH monotherapy clinical trials, providing 3374 patient years of exposure to Dutasteride (Avodart<sup>®</sup>), there were 2 cases of breast cancer reported in Dutasteride (Avodart<sup>®</sup>)-treated patients, one after 10 weeks and one after 11 months of treatment and 1 case in a patient who received placebo. In subsequent clinical trials in BPH and 8231 men aged 50 to 75 with a prior negative biopsy for prostate cancer and baseline PSA between 2.5ng/mL and 10.0ng/mL providing 17489 patient years exposure to Dutasteride (Avodart<sup>®</sup>) and 5027 patient years exposure to Dutasteride (Avodart<sup>®</sup>) and tamsulosin combination there were no additional cases in any of the treatment groups. The relationship between long term use of dutasteride and male breast cancer is unknown.

#### **Pre-clinical Safety Data**

At exposures greatly in excess of those at the clinical dose, reversible, non-specific CNS-related effects were seen in rats (425-fold) and dogs (315-fold).

Other toxicity findings were consistent with the pharmacological activity of 5 alpha-reductase inhibition. In male rats and dogs, these included effects on accessory reproductive organs and, in male rats, a reversible decrease in fertility. This is considered to have no clinical relevance as there was no effect on sperm development, concentration or motility. Feminisation of the external genitalia was noted in male foetuses of female rats and rabbits orally dosed with dutasteride. However, intravenous administration of dutasteride to pregnant Rhesus monkeys during embryofoetal development at doses of up to 2010 nanogram/animal/day did not produce adverse maternal or foetal toxicity. This dose represents a multiple of at least 186-fold (nanogram/kg basis) the potential maximum daily dose in a 50 kg woman, resulting from exposure to 5 mL semen (assuming 100% absorption) from a dutasteride-treated man.

Dutasteride was not genotoxic in a wide range of mutagenicity tests.

In a carcinogenicity study in rats, there was an increase in benign interstitial cell tumours in the testis at the high dose (158-fold clinical exposure). However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans. There were no clinically relevant effects on tumour profile in a carcinogenicity study in mice.

## **INDICATIONS**

Dutasteride (Avodart<sup>®</sup>) treats and prevents progression of benign prostatic hyperplasia (BPH) through alleviating symptoms, reducing prostate size (volume), improving urinary flow rate and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery.

Dutasteride (Avodart<sup>®</sup>) in combination with the alpha-blocker tamsulosin, treats and prevents progression of benign prostatic hyperplasia (BPH) by reducing prostate size, alleviating symptoms, improving urinary flow and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery (see Clinical Studies).

## **DOSAGE & ADMINISTRATION**

### **Adult males (including elderly)**

Capsules should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa.

Dutasteride (Avodart<sup>®</sup>) may be taken with or without food.

The recommended dose of Dutasteride (Avodart<sup>®</sup>) is one capsule (0.5 mg) taken orally once a day.

Although an improvement may be observed at an early stage, treatment for at least 6 months may be necessary in order to assess objectively whether a satisfactory response to the treatment can be achieved.

For treatment of BPH, Dutasteride (*Avodart*<sup>®</sup>) can be administered alone or in combination with the alpha-blocker tamsulosin (0.4mg).

#### **Renal impairment**

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see *Pharmacokinetics*).

#### **Hepatic impairment**

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied (see *Warnings and Precautions and Pharmacokinetics*).

### **CONTRAINDICATIONS**

Dutasteride (*Avodart*<sup>®</sup>) is contraindicated in patients with known hypersensitivity to dutasteride, other 5- $\alpha$ -reductase inhibitors, or any component of the preparation.

Dutasteride (*Avodart*<sup>®</sup>) is contraindicated for use in women and children (see *Pregnancy and Lactation*).

### **WARNINGS & PRECAUTIONS**

Dutasteride (*Avodart*<sup>®</sup>) is absorbed through the skin, therefore women and children must avoid contact with leaking capsules (see *Pregnancy and Lactation*). If contact is made with leaking capsules the contact area should be washed immediately with soap and water.

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolised and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease (see *Dosage and Administration and Pharmacokinetics*).

#### **Combination Therapy with Tamsulosin and cardiac failure**

In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of Dutasteride (*Avodart*<sup>®</sup>) and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low ( $\leq 1\%$ ) and variable between the studies. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between Dutasteride (*Avodart*<sup>®</sup>) (alone or in combination with an alpha blocker) and cardiac failure has been established (see Clinical Studies).

#### **Effects on prostate specific antigen (PSA) and prostate cancer detection**

Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients prior to initiating therapy with dutasteride and periodically thereafter.

Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer.

Dutasteride (*Avodart*<sup>®</sup>) causes a decrease in mean serum PSA levels by approximately 50% after 6 months of treatment. Patients receiving Dutasteride (*Avodart*<sup>®</sup>) should have a new PSA baseline established after 6 months of treatment with Dutasteride (*Avodart*<sup>®</sup>). It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA levels while on Dutasteride (*Avodart*<sup>®</sup>) may signal the presence of prostate cancer (particularly high grade cancer) or non-compliance to therapy with Dutasteride (*Avodart*<sup>®</sup>) and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5 $\alpha$ -reductase inhibitor (see Clinical Studies). In the interpretation of a PSA value for a patient taking Dutasteride (*Avodart*<sup>®</sup>), previous PSA values should be sought for comparison.

Treatment with Dutasteride (*Avodart*<sup>®</sup>) does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established (see Clinical Studies).

Total serum PSA levels return to baseline within 6 months of discontinuing treatment.

The ratio of free to total PSA remains constant even under the influence of Dutasteride (*Avodart*<sup>®</sup>). If clinicians elect to use percent-free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary.

#### **Prostate cancer and high grade tumours**

In a 4-year study of over 8,000 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5ng/mL and 10.0ng/mL (the REDUCE study), 1,517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8-10 prostate cancers in the Dutasteride (*Avodart*<sup>®</sup>) group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers. No causal relationship between Dutasteride (*Avodart*<sup>®</sup>) and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking Dutasteride (*Avodart*<sup>®</sup>) should be regularly evaluated for prostate cancer risk including PSA testing (see Clinical Studies).

#### **Breast cancer in men**

Breast cancer has been reported in men taking dutasteride in clinical trials (see Clinical Studies) and during the post-marketing period. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. It is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

### **DRUG INTERACTIONS**

*In vitro* drug metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4.

Phase II data showed a decrease in clearance of dutasteride when co-administered with the CYP3A4 inhibitors verapamil (37%) and diltiazem (44%). In contrast no decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride. A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10-times the recommended dose has been given to patients for up to six months), therefore no dose adjustment is necessary.

*In vitro*, dutasteride is not metabolized by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6.

Dutasteride neither inhibits human cytochrome P450 drug-metabolizing enzymes *in vitro* nor induces cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A in rats and dogs *in vivo*.

*In vitro* studies demonstrate that dutasteride does not displace warfarin, diazepam, acenocoumarol, phenprocoumon, or phenytoin from plasma protein, nor do these model compounds displace dutasteride. Compounds that have been tested for drug interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant pharmacokinetic or pharmacodynamic interactions have been observed.

Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in large Phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered 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.

## PREGNANCY AND LACTATION

### Fertility

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%), two 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.

### Pregnancy

Dutasteride is contraindicated for use by women. Dutasteride has not been studied in women because pre-clinical data suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman exposed to dutasteride.

### Lactation

It is not known whether dutasteride is excreted in breast milk.

### Effects on Ability to Drive and Use Machines

Based on the pharmacokinetic and pharmacodynamic properties of dutasteride treatment with dutasteride would not be expected to interfere with the ability to drive or operate machinery.

## ADVERSE REACTIONS

### Clinical Trial Data

#### Dutasteride (Avodart®) Monotherapy for BPH

The following investigator-judged drug-related adverse events (with incidence ≥1%) have been reported more commonly in the three phase III placebo controlled studies on Dutasteride (Avodart®) treatment compared to placebo:

| Adverse event               | Incidence during year 1 of treatment |  | Incidence during year 2 of treatment |  |
|-----------------------------|--------------------------------------|--|--------------------------------------|--|
|                             | Placebo<br>(n= 2158)                 | Dutasteride<br>(Avodart®)<br>(n= 2167) | Placebo<br>(n= 1736)                 | Dutasteride<br>(Avodart®)<br>(n= 1744) |
| Impotence*                  | 3%                                   | 6%                                     | 1%                                   | 2%                                     |
| Altered (decreased) libido* | 2%                                   | 4%                                     | <1%                                  | <1%                                    |
| Ejaculation disorders*      | <1%                                  | 2%                                     | <1%                                  | <1%                                    |
| Breast disorders +          | <1%                                  | 1%                                     | <1%                                  | 1%                                     |

\* These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.

+ includes breast tenderness and breast enlargement

No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

#### Dutasteride (Avodart®) and Tamsulosin Combination Therapy for BPH

The following investigator-judged drug-related adverse events (with a cumulative incidence of greater than or equal to 1%) have been reported in the CombAT (Combination of Dutasteride (Avodart®) and Tamsulosin) Study, a comparison of Dutasteride (Avodart®) 0.5mg and tamsulosin 0.4mg once daily for four years in combination or as monotherapy.

| Adverse Reaction                        | Incidence during treatment period |          |          |          |
|---|-----------------------------------|----------|----------|----------|
|   | Year 1                            | Year 2   | Year 3   | Year 4   |
| Combination <sup>a</sup> (n)            | (n=1610)                          | (n=1428) | (n=1283) | (n=1200) |
| Dutasteride                             | (n=1623)                          | (n=1464) | (n=1325) | (n=1200) |
| Tamsulosin                              | (n=1611)                          | (n=1468) | (n=1281) | (n=1112) |
| Impotence <sup>b</sup>                  |                                   |          |          |          |
| Combination <sup>a</sup>                | 6%                                | 2%       | <1%      | <1%      |
| Dutasteride                             | 5%                                | 2%       | <1%      | <1%      |
| Tamsulosin                              | 3%                                | 1%       | <1%      | 1%       |
| Altered (decreased) libido <sup>b</sup> |                                   |          |          |          |
| Combination <sup>a</sup>                | 5%                                | <1%      | <1%      | 0%       |
| Dutasteride                             | 4%                                | 1%       | <1%      | 0%       |
| Tamsulosin                              | 2%                                | <1%      | <1%      | <1%      |
| Ejaculation disorders <sup>b</sup>      |                                   |          |          |          |
| Combination <sup>a</sup>                | 9%                                | 1%       | <1%      | <1%      |
| Dutasteride                             | 1%                                | <1%      | <1%      | <1%      |
| Tamsulosin                              | 3%                                | <1%      | <1%      | <1%      |
| Breast disorders <sup>c</sup>           |                                   |          |          |          |
| Combination <sup>a</sup>                | 2%                                | <1%      | <1%      | <1%      |
| Dutasteride                             | 2%                                | 1%       | <1%      | <1%      |
| Tamsulosin                              | <1%                               | <1%      | <1%      | 0%       |
| Dizziness                               |                                   |          |          |          |
| Combination <sup>a</sup>                | 1%                                | <1%      | <1%      | <1%      |
| Dutasteride                             | <1%                               | <1%      | <1%      | <1%      |
| Tamsulosin                              | 1%                                | <1%      | <1%      | 0%       |

<sup>a</sup> Combination = dutasteride 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

<sup>b</sup> These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.

<sup>c</sup> Includes breast tenderness and breast enlargement.

#### Postmarketing Data

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ) and very rare ( $< 1/10,000$ ) including isolated reports. Frequency categories determined from post-marketing data refer to reporting rate rather than true frequency.

#### Immune system disorders

Very rare: Allergic reaction, including rash, pruritus, urticaria, localised oedema and angioedema.

#### Psychiatric disorders

Very rare: Depressed mood

#### Skin and subcutaneous tissue disorders

Rare: Alopecia (primarily body hair loss), Hypertrichosis

#### Reproductive system and breast disorders

Very rare: Testicular pain and testicular swelling

### OVERDOSAGE

In volunteer studies single doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In clinical studies doses of 5 mg daily have been administered to patients 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 overdose, symptomatic and supportive treatment should be given as appropriate.

### STORAGE CONDITIONS

Store at temperatures not exceeding 30°C

### AVAILABILITY

Dutasteride (Avodart<sup>®</sup>) 500 mcg Softgel Capsule is available in PVC/PVdC blister pack of 10's (Box of 30's).

### CAUTION

Foods, Drugs and Devices, and Cosmetics Acts prohibits dispensing without prescription.

Keep all medicines out of reach of children.

AVODART is a registered trademark of the GlaxoSmithKline group of companies.

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