Avodart®

Version number: GDS20/IPI17

Avodart®

Dutasteride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for oral use contains 0.5 mg dutasteride (*see List of Excipients*).

PHARMACEUTICAL FORM

Capsules: dull yellow in colour, opaque, oblong soft gelatin capsules marked with GX CE2.

CLINICAL PARTICULARS

Indications

AVODART® 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 BPHrelated surgery.

AVODART® in combination with the alphablocker 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 and 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.

AVODART® may be taken with or without food.

The recommended dose of *AVODART*® 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, *AVODART*® can be administered alone or in combination with the alpha-blocker tamsulosin (0.4 mg).

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

AVODART® is contraindicated in patients with known hypersensitivity to dutasteride, other 5 alphareductase inhibitors, or any component of the preparation (*see List of Excipients*).

AVODART® is contraindicated for use in women and children (*see Pregnancy and Lactation*).

Warnings and Precautions

Prostate cancer

In a 4-year study of over 8000 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), 1517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8-10 prostate cancers in the *AVODART*® 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 *AVODART*® and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking *AVODART*® should be regularly evaluated for prostate cancer risk including PSA testing.

In an additional 2-year follow-up study with the original patients from the dutasteride chemoprevention study (REDUCE), a low rate of new prostate cancers were diagnosed (dutasteride [n=14, 1.2%] and placebo [n=7, 0.7%]), with no new identified cases of Gleason 8–10 prostate cancers.

Long-term follow up (up to 18 years) of another 5-ARI (finasteride) in a chemoprevention study showed no statistically significant difference between finasteride and placebo in the rates of overall survival (HR 1.02, 95% CI 0.97-1.08) or survival after prostate cancer diagnoses (HR 1.01, 95% CI 0.85-1.20).

Prostate specific antigen (PSA)

Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer. *AVODART*® causes a decrease in mean serum PSA levels by approximately 50% after 6 months of treatment.

Patients receiving *AVODART*® should have a new PSA baseline established after 6 months of treatment with *AVODART*®. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on *AVODART*® may signal the presence of prostate cancer or non-compliance to therapy with *AVODART*® and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-ARI. In the interpretation of a PSA value for a patient taking *AVODART*®, previous PSA values should be sought for comparison. Treatment with *AVODART*® 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.

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 *AVODART*®. If clinicians elect to use percentfree PSA as an aid in the detection of prostate cancer in men undergoing *AVODART*® therapy, no adjustment to its value is necessary.

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

Cardiovascular adverse events

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 *AVODART*® 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 (≤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 *AVODART*® (alone or in combination with an alpha blocker) and cardiac failure has been established (*see Clinical Studies*).

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18802) that evaluated the risks of developing cardiovascular adverse events from the use of *AVODART*® (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1.05; 95% CI 0.71, 1.57), acute myocardial infarction (RR 1.00; 95% CI 0.77, 1.30) or stroke (RR 1.20; 95% CI 0.88, 1.64) were found.

Breast cancer

There have been rare reports of male breast cancer reported in men taking *AVODART*® in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5ARIs (*see Clinical Studies*). Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

Leaking capsules

Dutasteride 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.

Hepatic impairment

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*).

Interactions

In vitro drug metabolism studies show that dutasteride is metabolised by human cytochrome P_{450} 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 coadministered 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 10times the recommended dose has been given to patients for up to six months), therefore no dose adjustment is necessary.

In vitro, dutasteride is not metabolised by human cytochrome P_{450} isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6.

Dutasteride neither inhibits human cytochrome P_{450} drug-metabolizing enzymes *in vitro* nor induces cytochrome P_{450} isoenzymes CYP1A, CYP2B, and CYP3A in rats and dogs *in vivo.*

In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam, acenocoumorol, 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 coadministered with antihyperlipidemics, angiotensinconverting enzyme (ACE) inhibitors, betaadrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal antiinflammatory 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 preclinical 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

***AVODART*® Monotherapy for BPH**

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

Adverse event	Incidence during year 1 of treatment		Incidence during year 2 of treatment	
	Placebo (n=2158)	*AVODART*® (n=2167)	Placebo (n=1736)	*AVODART*® (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.

***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 *AVODART*® and Tamsulosin) Study, a comparison of *AVODART*® 0.5 mg and tamsulosin 0.4 mg 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[a] (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[b]				
Combination[a]	6%	2%	<1%	<1%
Dutasteride	5%	2%	<1%	<1%
Tamsulosin	3%	1%	<1%	1%
Altered (decreased) libido[b]				
Combination[a]	5%	<1%	<1%	0%
Dutasteride	4%	1%	<1%	0%
Tamsulosin	2%	<1%	<1%	<1%
Ejaculation disorders[b]				
Combination[a]	9%	1%	<1%	<1%
Dutasteride	1%	<1%	<1%	<1%
Tamsulosin	3%	<1%	<1%	<1%
Breast disorders[c]				
Combination[a]	2%	<1%	<1%	<1%
Dutasteride	2%	1%	<1%	<1%
Tamsulosin	<1%	<1%	<1%	0%
Dizziness				
Combination[a]	1%	<1%	<1%	<1%
Dutasteride	<1%	<1%	<1%	<1%
Tamsulosin	1%	<1%	<1%	0%

[a]Combination=dutasteride 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

[b]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.

[c]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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000) and very rare (<1/10000) including isolated reports. Frequency categories determined from postmarketing data refer to reporting rate rather than true frequency.

Immune system disorders

Very rare: Allergic reactions, 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

Overdose

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 overdosage, symptomatic and supportive treatment should be given as appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Dutasteride is a dual inhibitor of 5 alphareductase. It inhibits both type 1 and type 2, 5 alphareductase 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 *AVODART*® on the reduction on DHT is dosedependent and is observed within 1 to 2 weeks. After 1 week and 2 weeks of daily dosing of *AVODART*® 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 alphareductase 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 to3 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_{ss}) 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 P_{450} isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolised by CYP1A2, CY2A6, 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 nonsaturable (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_{max} 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

***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, placebocontrolled, double-blind studies.
In men with BPH, *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 improved for a further 2 years in openlabel extension studies. In addition, reductions in prostate volume were sustained for a further 2 years in open-label extension studies.

***AVODART*® and tamsulosin combination therapy for BPH**
AVODART® 0.5 mg/day, tamsulosin 0.4 mg/day or the combination of *AVODART*® 0.5 mg plus tamsulosin 0.4 mg 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 *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 *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 *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 *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 *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 *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 *AVODART*® monotherapy and -3.8 units for tamsulosin monotherapy.
After 4 years of treatment, the adjusted mean improvement in flow rate (Q_{max}) from baseline was 2.4 ml/sec for combination therapy, 2.0 ml/sec for *AVODART*® monotherapy and 0.7 ml/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Q_{max} was statistically significantly greater with combination therapy at each 6 month assessment from Month 6 to Month 48 (p<0.001). Compared with *AVODART*®, the adjusted mean improvement from baseline in Q_{max} 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 *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 *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 *AVODART*® coadministered with tamsulosin and dutasteride or 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: *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 *AVODART*® monotherapy and 1.36 [95% CI 0.61, 3.07] compared to tamsulosin monotherapy.
In a 4-year chemoprevention, comparison study of placebo and *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 *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 *AVODART*® and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking *AVODART*® and an alpha blocker concomitantly: *AVODART*® 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 *AVODART*® (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 *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), 6706 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 *AVODART*® 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 *AVODART*® 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 *AVODART*® 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 *AVODART*® 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 *AVODART*® 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 *AVODART*®, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy (*see Warnings and Precautions*).
The results of an epidemiological, population-based study (n=174895) in community practice settings show that the use of 5-ARIs to treat BPH/LUTS is not associated with an increased risk of prostate cancer mortality (hazard ratio adjusted for competing risks: 0.85, 95% CI 0.72, 1.01) when compared with the use of alphablockers. Similar results were reported in an epidemiological study (n=13892) of men with prostate cancer in the UK (adjusted hazard ratio for prostate cancer mortality for 5-ARI users versus non-users: 0.86; 95% CI 0.69, 1.06). A prospective cohort study, the Health Professional's Follow-up Study (n=38058), also found that 5-ARI use was not associated with fatal prostate cancer (adjusted HR: 0.99; 95% CI 0.58, 1.69).

Effects on prostate specific antigen (PSA) and prostate cancer detection
In the REDUCE study, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL, *AVODART*® 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 *AVODART*®, there were 2 cases of male breast cancer reported in *AVODART*® -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 2.5 ng/mL and 10.0 ng/mL providing 17489 patient years exposure to *AVODART*® and 5027 patient years exposure to *AVODART*® and tamsulosin combination there were no reported breast cancer cases in any of the treatment groups.
Two case control, epidemiological studies, one conducted in a US (n=339 breast cancer cases and n=6780 controls) and the other in a UK (n=338 breast cancer cases and n=3930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5ARIs (*see Warnings and Precautions*). Results from the first study did not identify a positive association for male breast cancer (relative risk for ≥1-year of use before breast cancer diagnosis compared with <1-year of use: 0.70: 95% CI 0.34, 1.45). In the second study, the estimated odds ratio for breast cancer associated with the use of 5-ARIs compared with non-use was (1.08: 95% CI 0.62, 1.87).
The relationship between long term use of dutasteride and male breast cancer has not been established.

Pre-clinical Safety Data
At exposures greatly in excess of those at the clinical dose, reversible, nonspecific CNS-related effects were seen in rats (425-fold) and dogs (315-fold).
Other toxicity findings were consistent with the pharmacological activity of 5 alphareductase 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.

PHARMACEUTICAL PARTICULARS

List of Excipients
Capsule contents: monodiglycerides of caprylic/capric acid; butylated hydroxytoluene
Capsule shell: gelatin; glycerol; titanium dioxide (E171, CI 77891); iron oxide yellow (E172, CI 77492).
Medium chain triglycerides and lecithin as capsule lubricants.

Incompatibilities
Not applicable.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Do not store above 30°C.

Nature and Contents of Container
PVC/PVDC blisters.

Instructions for Use/Handling
Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules *(see Warnings and Precautions and Pregnancy and Lactation*). If contact is made with leaking capsules the contact area should be washed immediately with soap and water.
Not all presentations are available in every country.

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