AUSTRALIAN PI – AVODART (DUTASTERIDE) SOFT CAPSULES

1 NAME OF THE MEDICINE

Dutasteride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dutasteride 500 μg.

Excipients with known effect

Lecithin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Yellow, opaque, oblong, soft gelatin capsules marked with GX CE2.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AVODART is indicated for use as monotherapy for the management of symptomatic benign prostatic hyperplasia (BPH) or as combination therapy with an alpha blocker which is approved for use in BPH and which has been dose titrated in accordance with the relevant recommendations in the product information for that alpha blocker.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dutasteride can be administered alone or in combination with an alpha blocker.

Adult males (including elderly)

The recommended dose is one 500 μg capsule daily. 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 taken with or without food.

Although early improvements in symptoms may be seen in some patients, treatment for at least 6 months is generally necessary to assess whether a beneficial response in symptom relief has been achieved.

Dosage in 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 Section 5.2 PHARMACOKINETIC PROPERTIES).

Dosage in hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES). The use of dutasteride in patients with severe hepatic impairment is contraindicated.

Combination use with an alpha blocker

Implementation of the combination therapy of AVODART and an alpha blocker requires consideration of the combined side-effect profiles. Cardiovascular function should be stabilised prior to initiating combination therapy or adding an alpha blocker to AVODART monotherapy. When initiating less selective alpha blockers such as doxazosin, terazosin and prazosin, careful and measured titration of the dose is required to minimise the risk of alpha blocker-related adverse events such as postural hypotension, dizziness, and syncope. Dose titration is normally not required for the selective alpha blockers such as tamsulosin and alfuzosin. Please see the recommendations in the product information of the relevant alpha blocker for full safety information.

4.3 CONTRAINDICATIONS

AVODART is contraindicated in:

- patients with known hypersensitivity to dutasteride, other 5-alpha-reductase inhibitors, or any component of the preparation.
- women and children (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric use and Section 4.6 FERTILITY, PREGNANCY AND LACTATION).
- patients with severe hepatic impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prostate cancer

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 2.5 ng/mL and 10.0 ng/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 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 and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking dutasteride should be regularly evaluated for prostate cancer risk including PSA testing (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials).

In an additional 2-year follow-up study of the original patients from the dutasteride 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 except in one case from the former dutasteride treatment group where local pathology review reported a Gleason 8 case and central pathology review was not available. Dutasteride treatment was not provided during the follow-up study period but patients from either treatment arm were able to take 5-ARI therapy if prescribed.

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 with BPH 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.

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 (particularly high grade 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 5ARI (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials). 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 percent free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary.

Cardiovascular adverse events

Implementation of the combination therapy of AVODART and an alpha blocker requires consideration of the combined side-effect profiles. Cardiovascular function should be stabilised prior to initiating combination therapy or adding an alpha blocker to AVODART monotherapy. When initiating less selective alpha blockers such as doxazosin, terazosin and prazosin, careful and measured titration of the dose is required to minimise the risk of alpha blocker-related adverse events such as postural hypotension, dizziness, and syncope. Dose titration is normally not required for the selective alpha blockers such as tamsulosin and alfuzosin. Please see the recommendations in the product information of the relevant alpha blocker for full safety information.

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 and an alpha blocker, (primarily tamsulosin, alfuzosin, doxazosin and terazosin) than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was ≤1%. The reason for the imbalance of cardiac failure in the two trials is not known. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials).

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18,802) that evaluated the risks of developing cardiovascular adverse events from the use of dutasteride (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. The relationship between dutasteride use and the cardiovascular adverse events heart failure, acute myocardial infarction and stroke is unclear.

Breast cancer

There have been reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no statistically significant increase in the risk of developing male breast cancer with the use of 5-ARIs (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials). 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.

Leaking capsules

Dutasteride is absorbed through the skin, therefore, women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy and Use in lactation).

Blood donation

Men being treated with AVODART 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.

Use in hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Dutasteride is extensively metabolised and has a half-life of 3 to 5 weeks, therefore caution should be used in the administration of dutasteride to patients with liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Paediatric use

The use of dutasteride is contraindicated in children. Dutasteride has not been studied in children.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interactions of clinical significance have been identified.

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 metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6.

Dutasteride neither inhibits the *in vitro* metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4), 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, acenocoumorol, phenprocoumon, diazepam, 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of dutasteride 500 µg/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.

Treatment of sexually mature male rats with dutasteride at doses up to 500 mg/kg/day (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 (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 were detected in the serum of untreated female rats mated to males dosed at 10 mg/kg/day and above for 29 weeks.

In rats and dogs, repeated oral administration of dutasteride resulted in some animals showing signs of non-specific, reversible, centrally mediated toxicity, without associated changes at exposures 207 and 314 fold the expected clinical exposure of the dutasteride, respectively.

Use in pregnancy

(Pregnancy Category X)

AVODART is contraindicated for use in women. AVODART 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 fetus carried by a woman exposed to dutasteride.

In an intravenous embryo-fetal development study in the rhesus monkey, administration of dutasteride at doses up to 2010 ng/day on gestation days 20 to 100 did not adversely affect development of male external genitalia. Reduction of fetal adrenal weights, reduction of fetal prostate weights, and increases in fetal ovarian and testes weights were observed in monkeys treated with the highest doses. Based on the highest measured semen concentration of dutasteride in treated men (14 ng/mL), these doses are approximately 16 times (based on blood levels of parent drug; 186-fold based on daily dose in ng/kg of body weight) the potential maximum exposure of a 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 up to 30 mg/kg/day resulted in feminisation of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses (0.09- to 143-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 (18- to 143-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 (70- to 143-fold the expected clinical exposure).

In an oral pre- and post-natal development study in rats, dutasteride doses up to 30 mg/kg/day were administered. Feminisation 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 (15- to 109-fold the expected clinical exposure in men). At a daily dose of 0.05 mg/kg/day (0.06-fold the expected clinical exposure), evidence of feminisation 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 decreased 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. Feminisation of male fetuses is an expected physiological consequence of inhibition of the conversion of testosterone to DHT by 5α-reductase deficiency.

In the rabbit, embryo-fetal study doses up to 200 mg/kg/day (31- to 95-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 feminisation of the male fetus at all doses. It is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

Warnings:

Exposure of Women-Risk to Male Fetus: Dutasteride is absorbed through the skin. Therefore, women who are pregnant or may be pregnant should not handle AVODART Soft Gelatin Capsules because of the possibility of absorption of dutasteride and the potential risk of a fetal anomaly to a male fetus (see Section 4.3 CONTRAINDICATIONS).

As with other 5α-reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male fetus, inhibit the development of the external genitalia of the fetus. Small amounts of dutasteride have been recovered from the semen in subjects receiving AVODART 500 µg day. Based on studies in animals, it is unlikely that a male fetus will be adversely affected if his mother is exposed to the semen of a patient being treated with AVODART (the risk of which is greatest during the first 16 weeks of pregnancy). However, as with all 5α-reductase inhibitors, when the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom.

Use in lactation

AVODART is contraindicated for use in women. It is not known if dutasteride is excreted in animal or human 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.

4.7 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Dutasteride Monotherapy for BPH

AVODART is well tolerated in men with BPH.

The nature and frequency of adverse reactions reported in the pivotal efficacy studies (ARIA3001, ARIA3002 and ARIB3003) were generally similar in patients treated with dutasteride or with placebo. Investigator-judged drug-related adverse events (with incidence more than or equal to 1%) reported more commonly in these studies on dutasteride treatment compared to placebo are presented in Table 1. A higher incidence of reproductive adverse reactions was reported in the dutasteride group, which was an expected class effect of 5α-reductase inhibitors. Overall, fewer adverse reactions were reported during the second year of treatment compared with the first year.

Table 1: Adverse reactions considered by the investigator to be attributable to study medication, occurring in ≥ 1% of patients and more frequently in the dutasteride than the placebo group in the three placebo-controlled studies (ARIA3001, ARIA3002 and ARIB3003) conducted over 2 years.

Adverse event	Year 1		Year 2	
	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

Dutasteride 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 dutasteride 500 µg and tamsulosin 400 µg once daily for four years in combination or as monotherapy.

Table 2 Investigator-judged drug-related adverse events

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)
Total incidence of drug-related adverse events				
Combination[a]	22%	6%	4%	2%
Dutasteride	15%	6%	3%	2%
Tamsulosin	13%	5%	2%	2%
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%

* Composite of similar event terms

[a] Combination = dutasteride 500 µg once daily plus tamsulosin 400 µg 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.

Post-marketing 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 (≥1/10,000 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

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.8 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 500 μg.

There is no specific antidote for dutasteride therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dutasteride inhibits the conversion of testosterone to 5α-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 two isoforms, type 1 and type 2. Studies *in vitro* have shown that dutasteride is a competitive inhibitor of both type 1 and type 2 5α-reductase isoenzymes.

Effects on DHT/Testosterone:

The maximum effect of daily doses of AVODART on the reduction on DHT is dose dependant and is observed within 1-2 weeks. After 1 week and 2 weeks of daily dosing of AVODART 500 μg, median serum DHT concentrations were reduced by 85% and 90% respectively

In BPH patients treated with 500 μg 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 5α-reductase inhibition and did not result in any known adverse events.

Clinical trials

Dutasteride monotherapy

The efficacy and safety of AVODART 500 μg/day in the treatment and prevention of progression of BPH in 4325 males (aged 47 to 94 years with BPH who had enlarged prostates (greater than 30 mL) and a PSA value within the range 1.5-10 ng/mL) was demonstrated in three pivotal, randomised, double-blind, placebo-controlled, 2-year multicentre studies (ARIA3001, ARIA3002 and ARIB3003). Of the 4325 males enrolled in the studies, 2167 received AVODART and 2158 received placebo.

Pooled data from the three pivotal studies show that, in men with BPH, AVODART reduces the risk of both acute urinary retention (AUR) and the need for surgical intervention (SI). Improvements in BPH related symptoms, increased maximum urinary flow rates, and decreasing prostate volume suggest AVODART reverses the progression of BPH in men with an enlarged prostate.

Pooled efficacy data from the three pivotal studies is summarised below:

Acute Urinary Retention (AUR) and Surgical Intervention:

Relative to placebo dutasteride significantly reduces both the risk and incidence of AUR by 57% (4.2% for placebo versus 1.8% for AVODART) and the need for BPH-related surgical intervention by 48% (4.1% for placebo versus 2.2% for AVODART) over 24 months.

Table 3 Rates of occurrence and risk reduction of urological events

Event	**Placebo (n = 2158)**	**AVODART (n = 2167)**	**Risk Reduction**
Acute urinary retention (AUR)	4.2% (n=90)	1.8% (n=39)	57% (p< 0.001)
BPH-related surgical intervention	4.1% (n=89)	2.2% (n=47)	48% (p<0.001)

Lower Urinary Tract Symptoms (LUTS) assessed by AUA-SI:

Symptoms were quantified using the AUA-SI (American Urological Association Symptom Index), a seven-item questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) by rating on a 0 to 5 scale with a maximum score of 35. Entry criteria included a screening score of ≥ 12 (moderate to severe symptoms). A reduction in score signifies an improvement in symptoms.

The AUA-SI results at each of the scheduled visits, pooled across the three pivotal studies (ARIA3001, ARIA3002, and ARIB3003), are presented in Figure 1. The baseline AUA-SI score across the three studies was approximately 17 units in both treatment groups. Statistically significant improvements in symptom score in patients treated with AVODART compared to placebo were noted from Month 6 through to Month 24 (p<0.001). At Month 24, the mean decrease from baseline in AUA-SI symptom scores was -4.8 units for dutasteride and -2.4 units for placebo.

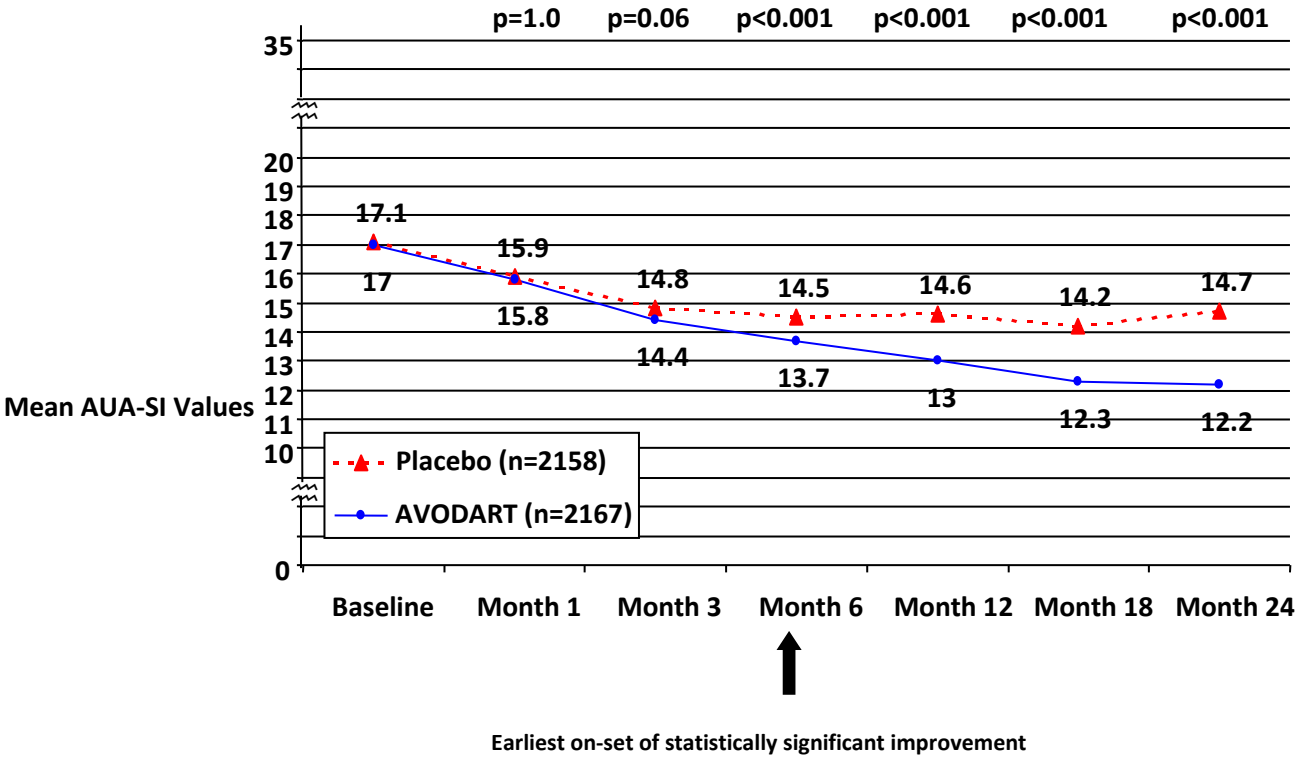


Figure 1: Pooled AUA-SI Mean Values (At Visit)

Maximum Urinary Flow (Qmax):

The Qmax results at each of the scheduled visits, pooled across the three pivotal studies (ARIA3001, ARIA3002, and ARIB3003), are presented in Figure 2. Baseline Qmax was approximately 10 mL/sec (normal Qmax ≥ 15 mL/sec) in both treatment groups across the three studies. Statistically significant improvement in Qmax in patients treated with AVODART compared to placebo was noted from Month 1 through to Month 24. At Month 24, treatment

urinary flow had improved by 0.8 mL/sec and 2.4 mL/sec in the placebo and AVODART groups respectively.

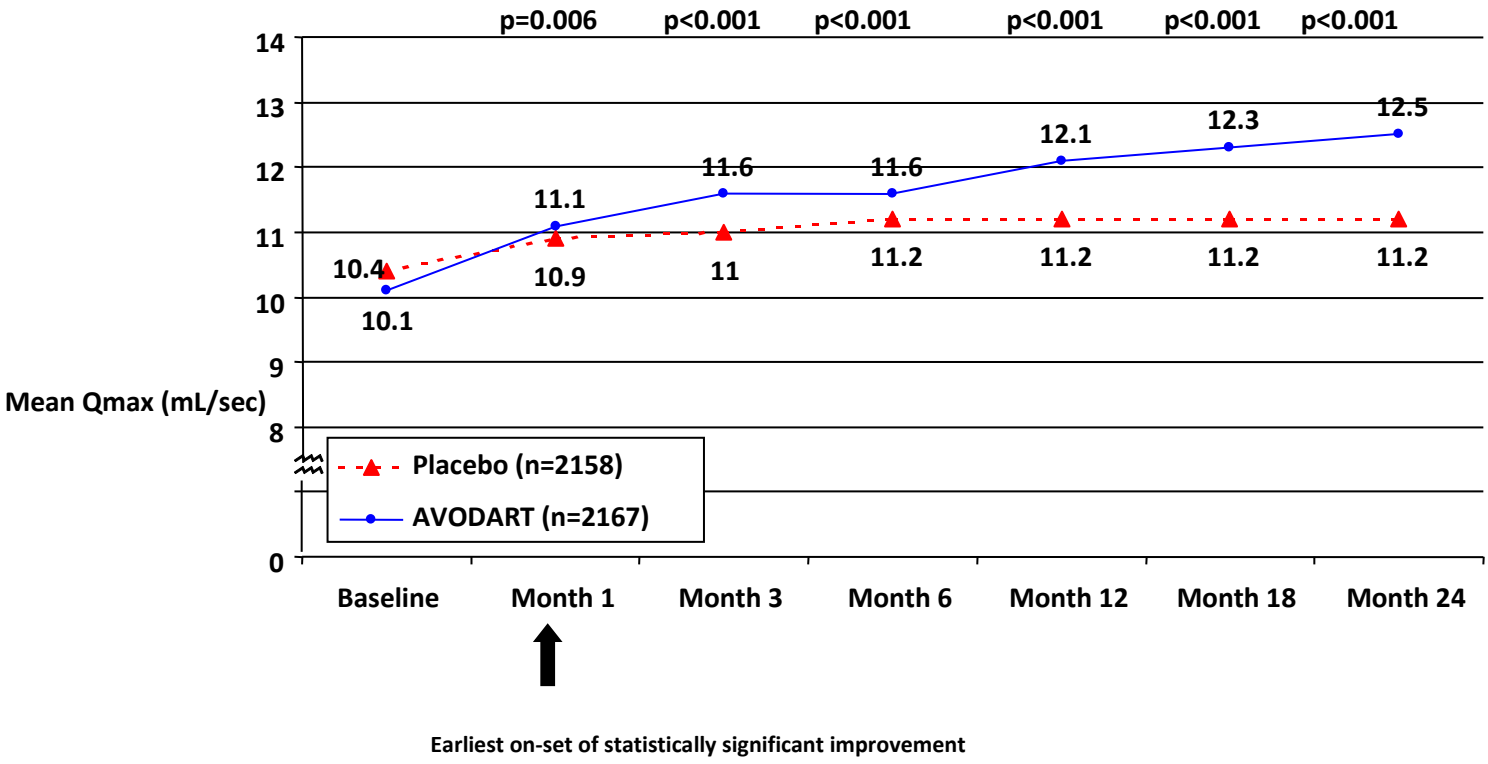


Figure 2: Pooled Maximum Urinary Flow (Qmax) Mean Values (mL/sec) (At Visit)

Prostate Volume:

In patients treated with AVODART, prostate volume was shown to reduce as early as one month after initiation of treatment and reductions continued through to Month 24 (p<0.001). AVODART led to a mean reduction of prostate volume of 23.6% (from 54.9 mL at baseline to 42.1 mL) at Month 12 compared with a mean reduction of 0.5% (from 54.0 mL to 53.7 mL) in the placebo group. At 24 months, AVODART decreased prostate volume by 25.7% (from 54.9 mL at baseline to 41.2 mL) compared with an increase of 1.7% (from 54.0 mL to 54.1 mL) in the placebo group.

Pooled safety data from the three pivotal studies show that the adverse reaction profile of dutasteride (500 μg/day for 24 months) was similar to that of placebo (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

<u>Dutasteride and tamsulosin combination therapy</u>

AVODART 500 μg/day (n=1,623), tamsulosin 400 μg/day (n=1,611) or the combination of AVODART 500 μg plus tamsulosin 400 μg (n=1,610) administered once daily [total number of patients = 4844] were evaluated in men with moderate to severe symptoms of BPH who had prostates ≥30 mL and a PSA values within the range 1.5 – 10 ng/mL in a multicenter, multinational, randomized double-blind, parallel group study (CombAT). Approximately 52%

of subjects had previous exposure to 5α-reductase inhibitor (5-ARI) or alpha-blocker treatment.

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 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 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 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.

Table 4 Results following 2 years of treatment

Parameter	**Time-point**	**Combination**	**Dutasteride**		**Tamsulosin**	
Primary endpoint				Adjusted mean difference (95%CI)		Adjusted mean difference (95%CI)
IPSS (units)	[Baseline] Month 24 (change from baseline)	[16.6] -6.2	[16.4] -4.9	-1.3 p<0.0001 (-1.69, -0.86)	[16.4] -4.3	-1.8 p<0.0001 (-2.23, -1.40)
Secondary endpoints						
Qmax (mL/sec)	[Baseline] Month 24 (change from baseline)	[10.9] 2.4	[10.6] 1.9	0.52 p=0.003 (0.18, 0.86)	[10.7] 0.9	1.53 p<0.001 (1.20, 1.87)
Prostate Volume	[Baseline] (mL) Month 24 (% change from baseline)	[54.7] -26.9	[54.6] -28.0	1.1 p=0.19 (-1.6, 2.8)	[55.8] 0.0	-26.9 p<0.001 (-28.9, -24.9)
Prostate Transition Zone Volume	[Baseline] (mL) Month 24 (% change from baseline)	[27.7] -23.4	[30.3] -22.8	-0.5 p=0.90 (-8.3, 7.2)	[30.5] 8.8	-32.1 p<0.001 (-42.6, -21.6)

BPH Impact Index (BII) (units)	[Baseline] Month 24 (change from baseline)	[5.3] -2.1	[5.3] -1.7	-0.34 p<0.0001 (-0.52, -0.16)	[5.3] -1.5	-0.62 p<0.001 (-0.80, -0.44)
IPSS Question 8 (BPH-related Health Status)	[Baseline] Month 24 (change from baseline)	[3.6] -1.4	[3.6] -1.1	-0.23 p<0.0001 (-0.32, -0.14)	[3.6] -1.1	-0.30 p<0.0001 (-0.39, -0.21)

The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH-related surgery. The study was powered to show a statistical difference between combination therapy and tamsulosin, but not between combination therapy and dutasteride or between tamsulosin and dutasteride. 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 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.

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 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 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 dutasteride 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 dutasteride, 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 dutasteride 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 units for dutasteride and -1.2 units for tamsulosin. The

adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 units for dutasteride and -1.1 units 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.

Table 5 Results following 4 years of treatment

Parameter	**Time-point**	**Combination**	**Dutasteride**		**Tamsulosin**	
Primary endpoint with study powered treatment comparison						Risk Reduction Estimate (95% CI)
Incidence of AUR or BPH Related Surgery	Month 48	4.2%			11.9%	65.8% p<0.001 (54.7%, 74.1%)
Other endpoints and treatment comparisons				Risk Reduction Estimate (95% CI)		Risk Reduction Estimate (95% CI)
Incidence of AUR or BPH Related Surgery	Month 48	4.2%	5.2%	19.6% p=0.18 (-10.9%, 41.7%)		
Clinical Progression*	Month 48	12.6%	17.8%	31.2% p<0.001 (17.7%, 42.5%)	21.5%	44.1% p<0.001 (33.6%, 53%)
				Adjusted mean difference (95%CI)		Adjusted mean difference (95%CI)
IPSS (units)	[Baseline] Month 48 (change from baseline)	[16.6] -6.3	[16.4] -5.3	-0.96 p<0.001 (-1.40, -0.52)	[16.4] -3.8	-2.5 p<0.001 (-2.96, -2.07)
Qmax (mL/sec)	[Baseline] Month 48	[10.9] 2.4	[10.6] 2.0	0.35 p=0.05	[10.7] -0.7	1.66 p<0.001

	(change from baseline)			(0.00, 0.70)		(1.31, 2.01)
Prostate Volume	[Baseline] (mL) Month 48 (% change from baseline)	[54.7] -27.3	[54.6] -28.0	0.7 p=0.42 (-1.1, 2.5)	[55.8] 4.6	-31.9 p<0.001 (-34.1, -29.7)
Prostate Transition Zone Volume	[Baseline] (mL) Month 48 (% change from baseline)	[27.7] -17.9	[30.3] -26.5	8.6 p=0.053 (-0.1, 17.4)	[30.5] 18.2	-36.1 p<0.001 (-47.9, -24.3)
BPH Impact Index (BII) (units)	[Baseline] Month 48 (change from baseline)	[5.3] -2.2	[5.3] -1.8	-0.32 p<0.001 (-0.51, -0.13)	[5.3] -1.2	-0.94 p<0.001 (-1.13, -0.75)
IPSS Question 8 (BPH-related Health Status)	[Baseline] Month 48 (change from baseline)	[3.6] -1.5	[3.6] -1.3	-0.23 p<0.001 (-0.32, -0.13)	[3.6] -1.1	-0.46 p<0.001 (-0.55, -0.37)

*Clinical progression was a composite measure defined as one of the following: symptom deterioration by International Prostate Symptom Score ≥4 points on two consecutive visits; BPH-related AUR; BPH-related urinary incontinence; recurrent BPH-related urinary tract infection or urosepsis; BPH-related renal insufficiency

Cardiac Failure

In a 4 year comparison of dutasteride 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: dutasteride, 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 monotherapy and 1.36 [95% CI 0.61, 3.07] compared to tamsulosin monotherapy. The reason for the observed imbalance is not known. There was no difference between treatment groups in incidence of overall cardiovascular events.

In REDUCE (a 4 year, double-blind, randomized parallel group study comparing dutasteride 500 μg/day or placebo in men at increased risk of developing prostate cancer), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride (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 (primarily tamsulosin, alfuzosin, doxazosin and terazosin), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking dutasteride and an alpha blocker concomitantly: dutasteride 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%). The reason

for the observed imbalance is not known. There was no difference between treatment groups in incidence of overall cardiovascular events. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Prostate cancer and high grade tumours

In a 4-year comparison of placebo and dutasteride 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), 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 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 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 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 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 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, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The results of a retrospective epidemiological, population-based study (n=174,895) in community practice settings based upon electronic health records 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 alpha-blockers. Similar results were reported in a retrospective epidemiological study (n=13,892) using electronic health records 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=38,058), also found that 5-ARI use was not associated with fatal prostate cancer (adjusted HR: 0.99; 95% CI 0.58, 1.69). The relationship between dutasteride use and prostate cancer mortality is unclear.

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

In the REDUCE study, a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL, dutasteride 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Breast neoplasia:

In dutasteride BPH monotherapy clinical trials, providing 3374 patient years of exposure to dutasteride, there were 2 cases of male breast cancer reported in dutasteride-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 dutasteride and 5027 patient years exposure to dutasteride 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=6,780 controls) and the other in a UK (n=338 breast cancer cases and n=3,930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5 ARIs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Results from the first study did not identify a positive association for male breast cancer (relative risk for $\geq$ 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 500 μg dose, peak serum concentrations of dutasteride occur within 1-3 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 (Css) of approximately 40 ng/mL are achieved after 6 months of dosing 500 μg 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 ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

Metabolism

Dutasteride is extensively metabolised in humans. While not all metabolic pathways have been identified, *in vitro* studies show that dutasteride is metabolised by the CYP3A4 isoenzyme to 2 minor mono-hydroxylated metabolites. Dutasteride is not metabolised *in vitro* by human cytochrome P450 isoenzymes CYP1A2, CY2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and 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), have been detected. *In vitro*, 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.

Excretion

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 500 μg/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

The elimination of dutasteride 500 μg appears to occur by two parallel, elimination pathways; one that is saturable at low concentrations and one that is not saturable. At serum levels greater than 3 ng/mL, including therapeutic concentrations, the slower, non-saturable elimination pathway dominates and dutasteride total clearance is linear with a half-life of 3 to 5 weeks.

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 to dutasteride, represented by AUC, was calculated to be higher in the middle age (50-69 years of age) and older age group ($\geq$ 70 years of age), compared to subjects 20-49 years of age. This difference was not statistically significant and no differences in drug effect as measured by DHT reduction were observed between age groups. On this basis no 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 500 μg 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The use of dutasteride in patients with severe hepatic impairment is contraindicated.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Dutasteride was not genotoxic in assays for gene mutations (in vitro tests for bacterial gene mutation) and chromosomal damage (chromosomal aberration in CHO cells in vitro and a micronucleus test in rats). Two of the major human metabolites were also negative in bacterial gene mutation assays.

Carcinogenicity

In a 2-year carcinogenicity study in B6C3F1 mice, at doses up to 500 mg/kg/day for males and 250 mg/kg/day for females, an increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (278-fold the expected clinical exposure to a 0.5 mg daily dose) in females only. Two of the three 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 up to 53 mg/kg/day for males and 15 mg/kg/day for females, there was an increase in Leydig cell adenomas in the testes at doses of 53 mg/kg/day (160-fold the expected clinical exposure). An increased incidence of Leydig cell hyperplasia was present at doses of 7.5 mg/kg/day (79-fold the expected clinical exposure) and above 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, there may have been limited exposure to the major human metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

AVODART soft capsules also contain the inactive ingredients butylated hydroxytoluene, gelatin, glycerol, iron oxide yellow, lecithin, medium chain triglycerides, mono- and di-glycerides, and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

AVODART capsules are available in blister packs of 10 (sample pack), 30 and 90 capsules.

Not all pack sizes may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

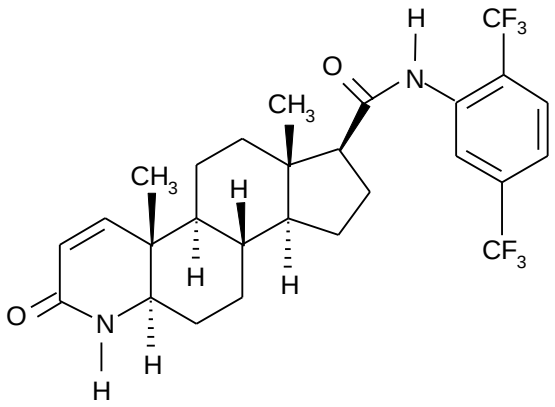
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name of dutasteride is 4-azaandrost-1-ene-17-carboxamide, N-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-, (5 alpha, 17 beta), with a molecular formula $C_{27}H_{30}F_6N_2O_2$ and a molecular weight of 528.5. Dutasteride is a white to pale yellow powder. It is insoluble in water, and soluble in organic solvents, dimethyl sulfoxide, acetone, methanol, ethanol and isopranol.

The chemical structure is:



CAS number

CAS Registry Number 164656-23-9.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI re-format and editorial updates
4.4	Updated information concerning prostate cancer, cardiovascular events and breast cancer
5.1	Updated information in Clinical trials section concerning prostate cancer, cardiovascular events and breast cancer

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