AUSTRALIAN PRODUCT INFORMATION – DUTATAM 500/400 (DUTASTERIDE/TAMSULOSIN HYDROCHLORIDE) CAPSULE, MODIFIED RELEASE

1 NAME OF THE MEDICINE

Dutasteride/tamsulosin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dutasteride 500 micrograms and tamsulosin hydrochloride 400 micrograms.

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

3 PHARMACEUTICAL FORM

DUTATAM 500/400 modified release capsules - Two piece, hard shell, size 00 capsules with an opaque yellow cap printed '640' with black ink and opaque white body, containing white to off white pellets and one white to off white soft gelatin capsule.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DUTATAM 500/400 is indicated for the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH).

4.2 DOSE AND METHOD OF ADMINISTRATION

DUTATAM 500/400 must be taken approximately 30 minutes after the same meal each day. Patients should be advised that DUTATAM 500/400 should not be taken on an empty stomach as this may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

For advice on switching from tamsulosin monotherapy to DUTATAM 500/400 combination therapy, please read the information under Section 5.1 PHARMACODYNAMIC PROPERTIES.

Populations

Adult males (including elderly)

The recommended dose of DUTATAM 500/400 is one capsule (500 micrograms dutasteride/400 micrograms tamsulosin) taken orally approximately 30 minutes after the same meal each day (see Section 5.2 PHARMACOKINETIC PROPERTIES – Absorption).

The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.

Renal impairment

The effect of renal impairment on dutasteride/tamsulosin hydrochloride pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES – Renal impairment). DUTATAM 500/400 is contraindicated in patients with severe renal impairment (see Section 4.3 CONTRAINDICATIONS).

Hepatic impairment

The effect of hepatic impairment on dutasteride/tamsulosin hydrochloride pharmacokinetics has not been studied (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES – Hepatic impairment). DUTATAM 500/400 is contraindicated in patients with severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

4.3 CONTRAINDICATIONS

DUTATAM 500/400 is contraindicated in:

- patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, tamsulosin hydrochloride or any component of the preparation.
- women and children (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).
- patients with a history of orthostatic hypotension
- patients with severe hepatic impairment (Child-Pugh scores >9).
- patients with severe renal impairment (creatinine clearance less than 10 mL/min).
- combination with another α_1-adrenergic blocker.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

DUTATAM 500/400 should be prescribed after careful benefit risk assessment and after consideration of alternative treatment options including monotherapies.

DUTATAM 500/400 must be taken approximately 30 minutes after the same meal each day (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Taking DUTATAM 500/400 on an empty stomach may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

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 to 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 DUTATAM 500/400 and periodically thereafter.

PSA concentration is an important component of the screening process to detect prostate cancer. Dutasteride causes a decrease in mean serum PSA levels by approximately 50% after 6 months of treatment.

Patients receiving DUTATAM 500/400 should have a new PSA baseline established after 6 months of treatment with dutasteride. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on DUTATAM 500/400 may signal the presence of prostate cancer (particularly high grade cancer) or non-compliance to therapy with DUTATAM 500/400 and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-ARI (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials). In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with DUTATAM 500/400 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 dutasteride. If clinicians elect to use percent-free PSA as an aid in the detection of prostate cancer in men undergoing DUTATAM 500/400 therapy, no adjustment to its value is necessary.

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 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.

Hypotension

As with other α1-adrenergic blockers, orthostatic hypotension can occur in patients treated with tamsulosin, which in rare cases can result in syncope.

There have been no studies to investigate the effect of dutasteride/tamsulosin hydrochloride on the ability to perform tasks that require judgement, motor or cognitive skills. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking DUTATAM 500/400.

Patients beginning treatment with DUTATAM 500/400 should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness and vertigo) until the symptoms have resolved and to report such symptoms without delay to their doctor. They should also be cautioned to avoid situations where injury could result should these symptoms occur.

Patients switching from the current Australian tamsulosin product should be advised of the differences between this product and DUTATAM 500/400 (see Section 5.2 PHARMACOKINETIC PROPERTIES) and the potential for orthostatic hypotension (particularly if DUTATAM 500/400 is taken on an empty stomach). Patients should be advised to take DUTATAM 500/400 approximately 30 minutes after the same meal each day and never on an empty stomach, as well as the need to maintain vigilance for signs of dizziness and vertigo.

Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with phosphodiesterase type 5 inhibitor (PDE5) inhibitors. Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Blood Donation

Men being treated with any dutasteride-containing products, including DUTATAM 500/400, 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.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients treated with α1-adrenergic blockers, including tamsulosin. This syndrome is characterised by the combination of a flaccid iris that billows as a result of intra-operative irrigation currents, prolapse of the iris toward the phaco-emulsification incisions, and progressive intra-operative miosis despite pre-operative dilation

with standard mydriatic drugs. IFIS may increase the risk of eye complications during and after operation.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with DUTATAM 500/400 in order to ensure that appropriate measures will be in place to manage IFIS if it occurs during surgery.

Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping of therapy prior to cataract surgery has not yet been established.

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 LACATION – Use in pregnancy and Use in lactation).

Inhibitors of CYP3A4 and CYP2D6

Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 (e.g. ketoconazole), or to a lesser extent, with strong inhibitors of CYP2D6 (e.g. paroxetine) can increase tamsulosin exposure (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor (e.g. erythromycin), a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Sulfur allergy

A causal relationship between tamsulosin and sulfur allergy has not been established, however there is a theoretical risk of an allergic reaction when tamsulosin is taken by patients with a history of sulfur allergy. If a patient reports a serious or life threatening sulfur allergy, caution is warranted when administering DUTATAM 500/400.

Use in 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

DUTATAM 500/400 is contraindicated in patients with severe hepatic impairment.

Use in renal impairment

Severe renal impairment, with creatinine clearance of less than 10 mL/min, is a CONTRAINDICATION, as these patients have not been studied.

Use in the elderly

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Paediatric use

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

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There have been no drug interaction studies for dutasteride/tamsulosin hydrochloride. The following statements reflect the information available on the individual components.

Interactions of dutasteride and tamsulosin with cytochrome P450 Inhibitors

Dutasteride: 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.

Long-term combination of dutasteride with drugs that are potent inhibitors of the enzyme CYP3A4 (e.g.ritonavir, indinavir, nefazodone, itraconazole, ketoconazole administered orally) may increase serum concentrations of dutasteride. Further inhibition of 5α-reductase at increased dutasteride exposure, is not likely. However, a reduction of the dutasteride dosing frequency can be considered if side effects are noted. It should be noted that in the case of enzyme inhibition, the long half-life may be further prolonged and it can take more than 6 months of concurrent therapy before a new steady state is reached.

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, CY2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6.

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

Tamsulosin: Strong and Moderate Inhibitor of CYP3A4 or CYP2D6: Tamsulosin is extensively metabolised, mainly by CYP3A4 or CYP2D6.

Concomitant treatment of tamsulosin hydrochloride and ketoconazole (a strong inhibitor of CYP3A4) resulted in an increase in the C_{max} and AUC of tamsulosin hydrochloride. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g., erythromycin) on the pharmacokinetics of tamsulosin have not been evaluated. Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) has also resulted in an increase of the C_{max} and AUC

of tamsulosin. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor. The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g. terbinafine) on the pharmacokinetics of tamsulosin have not been evaluated. The effects of concomitant administration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when tamsulosin 0.4 mg is coadministered with a combination of both CYP3A4 and CYP2D6 inhibitors. Tamsulosin hydrochloride is not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor (e.g. erythromycin), a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

Interactions of dutasteride and tamsulosin with particular drugs or classes of drugs

Cimetidine

Concomitant administration of tamsulosin hydrochloride (400 micrograms) and cimetidine (400 mg every 6 hours for 6 days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride-tamsulosin is used in combination with cimetidine.

Alpha-adrenergic Antagonists

There is a risk of additive hypotensive effects when tamsulosin hydrochloride is co-administered with drugs which can reduce blood pressure, including anaesthetic agents and other α_1-adrenergic blockers. Concurrent administration of DUTATAM 500/400 and other drugs containing α_1-adrenergic blockers is therefore contraindicated (see Section 4.3 CONTRAINDICATIONS).

PDE5 Inhibitors

Caution is advised when alpha-adrenergic antagonists, including tamsulosin-containing products such as DUTATAM 500/400 , are coadministered with PDE5 inhibitors. Alpha-adrenergic antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these 2 drug classes can potentially cause symptomatic hypotension.

Warfarin

Dutasteride: In vitro studies demonstrate that dutasteride does not displace warfarin. No clinically significant interactions have been observed following concomitant administration of dutasteride and tamsulosin.

Tamsulosin: A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

Nifedipine, Atenolol, Enalapril

Tamsulosin: In three studies, no interactions were seen when tamsulosin (400 micrograms for seven days followed by 800 micrograms for 7 days) was given concomitantly with atenolol, enalapril or nifedipine for 3 months; therefore no dose adjustments are necessary when these drugs are co-administered with DUTATAM 500/400 .

Digoxin and Theophylline

Dutasteride: Dutasteride does not alter the steady-state pharmacokinetics of digoxin.

Tamsulosin: Dosage adjustements are not necessary when tamsulosin is administered concomitantly with digoxin.

Concomitant administration of tamsulosin hydrochloride (400 micrograms/day for two days, followed by 800 micrograms/day for five to eight days) and a single i.v. dose of theophylline (5 mg/kg) resulted in no change in the pharmacokinetics of theophylline; therefore no dose adjustment is necessary.

Furosemide

Tamsulosin: Concomitant administration of tamsulosin hydrochloride (800 micrograms /day) and a single i.v. dose of furosemide (20 mg) produced an 11% to 12% reduction in the Cmax and AUC of tamsulosin hydrochloride, however these changes are expected to be clinically insignificant and no dose adjustment is necessary.

Calcium Channel Blockers

Dutasteride: Coadministration of verapamil or diltiazem decreases dutasteride clearance and leads to increased exposure to dutasteride. However, the change in dutasteride exposure is not considered clinically significant. No dosage adjustment of dutasteride is recommended.

Colestyramine

Dutasteride: Administration of a single 500 micrograms dose of dutasteride followed 1 hour later by a 12 g dose of colestyramine does not affect the relative bioavailability of dutasteride.

Other products

Dutasteride: In vitro studies demonstrate that dutasteride does not displace acenocoumorol, phenprocoumon, diazepam, or phenytoin from plasma protein, nor do these model compounds displace dutasteride.

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, non-steroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

A drug interaction study with tamsulosin or terazosin administered in combination with dutasteride for two weeks showed no evidence of pharmacokinetic or pharmacodynamic interactions.

Tamsulosin binds extensively to plasma proteins and may displace other protein-bound drugs. Conclusive clinical trials data are not available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There have been no studies to investigate the effect of dutasteride/tamsulosin hydrochloride on pregnancy, lactation and fertility. The following statements reflect the information available on the individual components.

Dutasteride

No animal fertility studies have been conducted with co-administration of dutasteride and tamsulosin.

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-dependant 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.

The effects of dutasteride 500 micrograms /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.

Tamsulosin

High doses of tamsulosin hydrochloride resulted in a reversible reduction in fertility in male rats considered possibly due to changes of semen content of impairment of ejaculation.
Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Use in pregnancy

(Pregnancy CategoryX)

DUTATAM 500/400 is contraindicated for use in women.

Dutasteride

As with other 5α-reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus. Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride. Based on studies in animals, it is unlikely that a male foetus will be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (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.

Tamsulosin

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits at higher than the therapeutic dose showed no evidence of foetal harm.

Use in lactation

DUTATAM 500/400 is contraindicated for use in women.

It is not known whether dutasteride or tamsulosin are excreted in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of dutasteride/tamsulosin hydrochloride on the ability to perform tasks that require judgement, motor or cognitive skills. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking DUTATAM 500/400.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

There have been no clinical trials conducted with dutasteride/tamsulosin hydrochloride; however, co-administration information for Years 1 and 2 is available from the CombAT (Combination of Avodart and Tamsulosin) study, a comparison of dutasteride 500 micrograms and tamsulosin 400 micrograms once daily for four years as co-administration or as monotherapy.

Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) is also provided.

Dutasteride and Tamsulosin Co-administration

Clinical Trial Data

The following investigator-judged drug-related adverse events (with a cumulative incidence of greater than or equal to 1%) have been reported during the CombAT study.

Table 1 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%

Adverse Reaction	Incidence during treatment period			
	Year 1	Year 2	Year 3	Year 4
Impotence*[b]				
Combination	6%	2%	<1%	<1%
Dutasteride	5%	2%	<1%	<1%
Tamsulosin	3%	1%	<1%	1%
Altered (decreased) libido* [b]				
Combination	5%	<1%	<1%	0%
Dutasteride	4%	1%	<1%	0%
Tamsulosin	2%	<1%	<1%	<1%
Ejaculation disorders* [b]				
Combination	9%	1%	<1%	<1%
Dutasteride	1%	<1%	<1%	<1%
Tamsulosin	3%	<1%	<1%	<1%
Breast disorders*[c]				
Combination	2%	<1%	<1%	<1%
Dutasteride	2%	1%	<1%	<1%
Tamsulosin	<1%	<1%	<1%	0%
Dizziness				
Combination	1%	<1%	<1%	<1%
Dutasteride	<1%	<1%	<1%	<1%
Tamsulosin	1%	<1%	<1%	0%

* Composite of similar event terms

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

Dutasteride Monotherapy

Clinical Trial Data

In three phase III placebo controlled studies of dutasteride treatment (n=2167) compared to placebo (n=2158), investigator-judged drug-related adverse events after one and two years of therapy were similar in type and frequency to those observed in the dutasteride monotherapy arm of the CombAT study (see table above).

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

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 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

Tamsulosin Monotherapy

Clinical Trial Data and Post marketing Data

Priapism

Rarely, tamsulosin, like other α_1-antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction.

Abnormal ejaculation

Patients should also be advised on the potential for abnormal ejaculation, such as retrograde ejaculation, to occur upon commencement of tamsulosin treatment.

The adverse reactions and frequency categories below relating to tamsulosin monotherapy are based on information available in the public domain. In the table below, common and uncommon reactions are consistent with those identified in a clinical trial setting and the frequency categories generally reflect incidence over placebo. Rare and very rare reactions are consistent with those identified from post marketing reports and the frequency categories reflect reporting rates.

	Frequency Category			
System Organ Class	Common (≥1/100 <1/10)	Uncommon (≥1/1000 <1/100)	Rare (≥1/10,000 <1/1000)	Very rare (<1/10,000) including isolated cases
Cardiac disorders		Palpitations		

Gastrointestinal disorders		Constipation Diarrhoea Vomiting		
General disorders and administration site disorders		Asthenia		
Nervous system disorders	Dizziness Insomnia		Syncope	
Reproductive system and breast disorders	Abnormal ejaculation			Priapism
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Immune system disorders		Rash Pruritis Urticaria	Angioedema	Stevens-Johnson Syndrome
Vascular disorders		Postural hypotension		

During post marketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with α_1-adrenergic blocker therapy; including tamsulosin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Infrequent reports of skin desquamation have also been received.

Post-marketing experience: In addition atrial fibrillation, arrhythmia, tachycardia dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative and dry mouth have been reported in association with tamsulosin use.

Reporting suspected adverse effects: 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.

4.9 OVERDOSE

No data are available with regard to overdosage of dutasteride/tamsulosin hydrochloride. The following statements reflect the information available on the individual components.

Dutasteride

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 micrograms.

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

Tamsulosin

In case of acute hypotension occurring after overdosage with tamsulosin hydrochloride cardiovascular support should be given. Restoration of blood pressure and normalization of heart rate may be accomplished by lying the patient down. If this is inadequate, administration of volume expanders and if necessary vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit in removing tamsulosin from the body.

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-tamsulosin is a combination of two drugs with complementary mechanisms of action to improve symptoms in patients with Benign Prostatic Hyperplasia (BPH): dutasteride, a dual 5α-reductase inhibitor (5-ARI) and tamsulosin hydrochloride, an antagonist of α_{1a}-adrenoreceptors.

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

Tamsulosin inhibits α_{1a} adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α_1-receptors in the prostate are of the α_{1a} subtype.

Pharmacodynamic Effects

The pharmacodynamic effects of dutasteride-tamsulosin as a fixed dose combination would not be expected to be different from those of dutasteride and tamsulosin co-administered as separate components.

Dutasteride

Dutasteride lowers DHT levels, reduces prostate volume, improves lower urinary tract symptoms and urine flow and reduces the risk of Acute Urinary Retention (AUR) and BPH-related surgery.

The maximum effect of daily doses of dutasteride on the reduction on DHT is dose-dependent and is observed within one to two weeks. After one week and two weeks of daily dosing of dutasteride 500 micrograms, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 500 micrograms of dutasteride daily, the median decrease in DHT was 94% at one year and 93% at two years, and the median increase in serum testosterone was 19% at both one and two years. This is an expected consequence of 5α-reductase inhibition and did not result in any known adverse events.

Tamsulosin

Tamsulosin increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role. Alpha-1 adrenergic blockers can reduce blood pressure by lowering peripheral resistance.

The tamsulosin hydrochloride (HCl) component in DUTATAM 500/400 has not been shown to be bioequivalent to the tamsulosin HCl product currently available in Australia. The clinical efficacy of the two tamsulosin formulations has been shown to be similar. Due to differences in pharmacokinetics, small differences in some adverse event rates have been reported.

When the Australian formulation of tamsulosin (tamsulosin OCAS 0.4 mg) was compared to a tamsulosin formulation equivalent to dutasteride 500 microgram and tamsulosin hydrochloride 400 microgram modified release capsule (tamsulosin MR 0.4 mg), the incidences of all treatment emergent adverse events attributable to α_1-adrenergic blockade were 6.9% (non-cardiovascular 4.4% and cardiovascular 2.5%) for the OCAS formulation and 7.8% (non-cardiovascular 5.1% and cardiovascular 3.2%) for the MR formulation. Non-cardiovascular events included all abnormal ejaculation-related events, headache, asthenia, fatigue, somnolence, rhinitis, nasal dryness, nasal congestion and nasal obstruction. Cardiovascular events included all dizziness-related events, palpitations, tachycardia, hypotension, orthostatic hypotension, dizziness postural, syncope, orthostatic/circulatory collapse and depressed level of/loss of consciousness. The most common treatment emergent adverse events were dizziness (1.4% vs 1.3%) and retrograde ejaculation (1.7% vs 1.4%). If switching between tamsulosin formulations, patients should be advised of these differences and monitored accordingly. Patients should also be reminded to adhere to the dosage and administration requirements for each product.

Clinical trials

Dutasteride co-administered with tamsulosin

The following statements reflect the information available on dutasteride and tamsulosin when administered together as separate medications.

Dutasteride 500 micrograms/day (n=1,623), tamsulosin 400 micrograms/day (n=1,611) or the combination of dutasteride 500 micrograms plus tamsulosin 400 micrograms (n=1,610) administered once daily [total number of patients = 4844] were evaluated in men with moderate to severe symptoms of BPH who had prostate volumes ≥30mL and Prostate Specific Antigen (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 5-alpha-reductase inhibitor 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).

The combination of dutasteride and tamsulosin provides superior improvement in symptoms than either component alone. After 2 years of treatment, co-administration 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 co-administration therapy, 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 co- administration therapy, -1.7 units for dutasteride and -1.5 units for tamsulosin. These improvements in flow rate and BII were statistically significant for co-administration therapy compared to both monotherapies.

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

Table 2 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 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. 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 (Qmax) 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 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, 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 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 3 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%)
Parameter	Time-point	Combination	Dutasteride		Tamsulosin	
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 (change from baseline)	[10.9] 2.4	[10.6] 2.0	0.35 p=0.05 (0.00, 0.70)	[10.7] -0.7	1.66 p<0.001 (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)

Parameter	Time-point	Combination	Dutasteride		Tamsulosin	
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.

Dutasteride monotherapy

The efficacy and safety of dutasteride 500 micrograms/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 dutasteride and 2158 received placebo.

Pooled data from the three pivotal studies show that, in men with BPH, dutasteride reduces the risk of both AUR and the need for surgical intervention (SI). Improvements in BPH related symptoms, increased maximum urinary flow rates, and decreasing prostate volume suggest dutasteride 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 dutasteride) and the need for BPH-related surgical intervention by 48% (4.1% for placebo versus 2.2% for dutasteride) over 24 months.

Table 4 Rates of occurrence and risk reduction of urological events

Event	**Placebo (n = 2158)**	**Dutasteride (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)

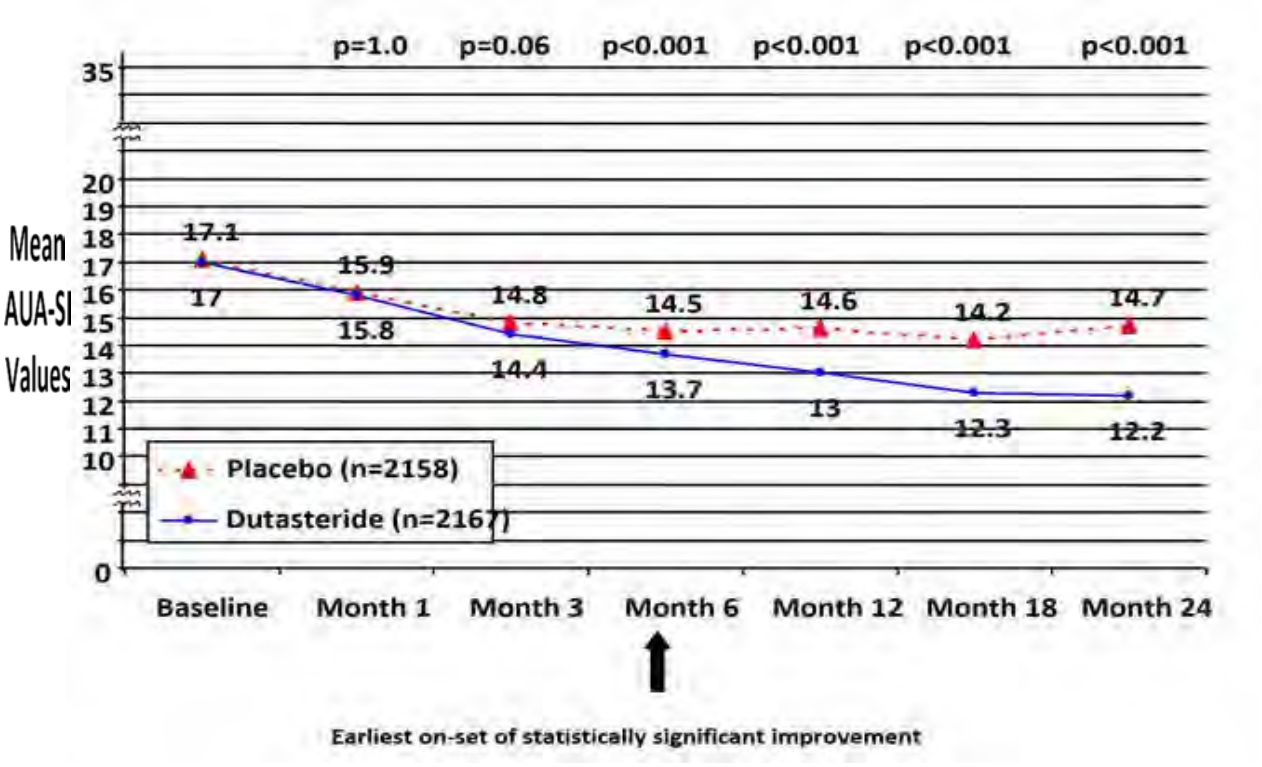
Lower Urinary Tract Symptoms (LUTS) assessed by AUA-SI:

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.

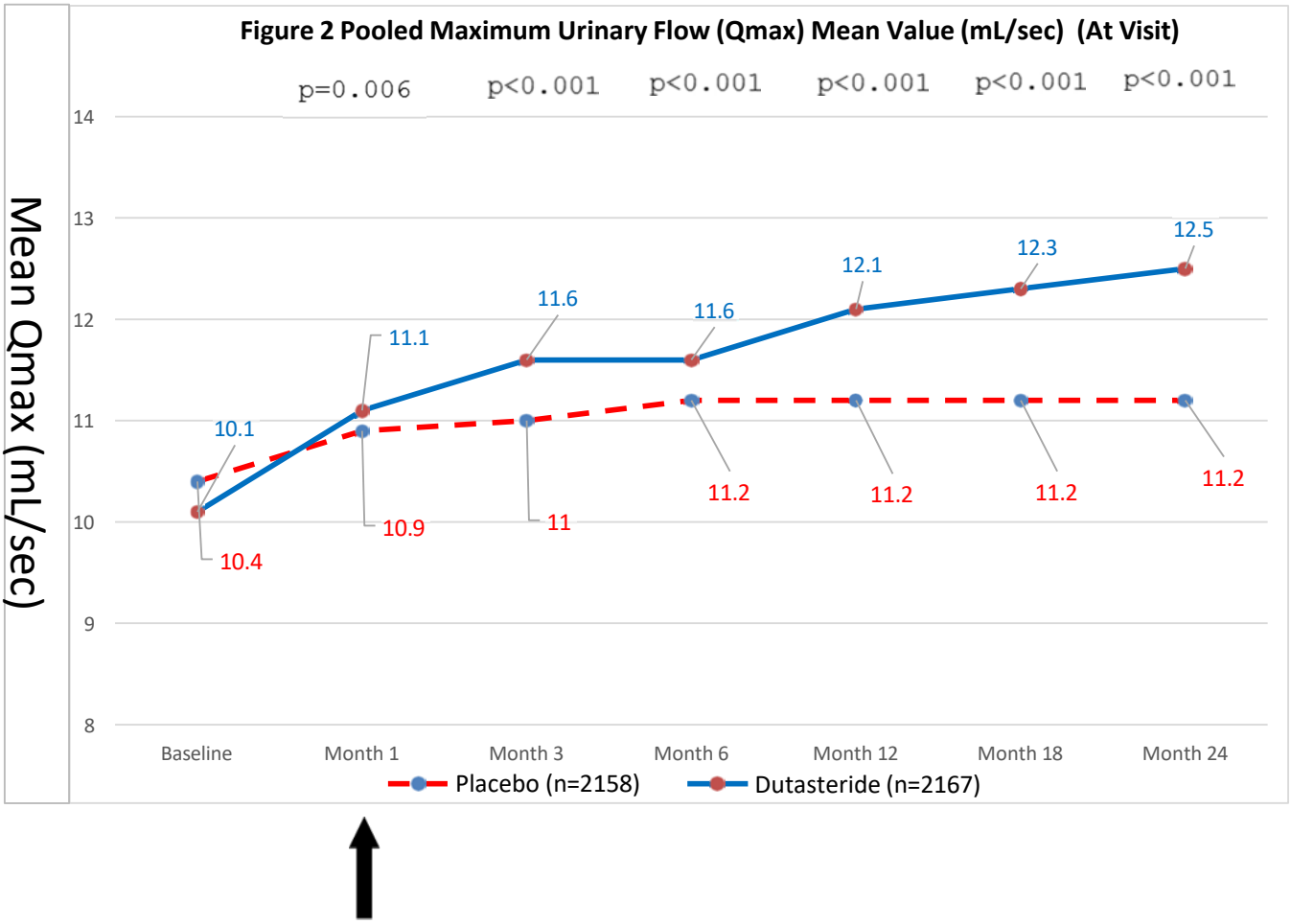
The AUA-SI results at each of the scheduled visits, pooled across the three pivotal studies (ARIA3001, ARIA3002, and ARIB3003), are presented in Figure 1. The baseline AUA-SI score across the three studies was approximately 17 units in both treatment groups. Statistically significant improvements in symptom score in patients treated with dutasteride 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 (Q_{max}):

The Q_{max} results at each of the scheduled visits, pooled across the three pivotal studies (ARIA3001, ARIA3002, and ARIB3003), are presented in Figure 2. Baseline Q_{max} was approximately 10 mL/sec (normal $Q_{max} \geq 15$ mL/sec) in both treatment groups across the three studies. Statistically significant improvement in Q_{max} in patients treated with dutasteride 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 dutasteride groups respectively.



Earliest on-set of statistically significant improvement

Prostate Volume:

In patients treated with dutasteride, prostate volume was shown to reduce as early as one month after initiation of treatment and reductions continued through to Month 24 ($p<0.001$). Dutasteride 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, dutasteride decreased prostate volume by 25.7% (from 54.9 mL at baseline to 41.2 mL) compared with an increase of 1.7% (from 54.0cc to 54.1cc) in the placebo group.

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

<u>Tamsulosin monotherapy</u>

Tamsulosin rapidly (from one week) increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role.

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 micrograms/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 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 developing 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

Bioequivalence was demonstrated between dutasteride 500 microgram and tamsulosin hydrochloride 400 microgram modified release capsule and concomitant dosing with separate dutasteride and tamsulosin capsules. (The formulation of tamsulosin used in these studies is not bioequivalent to the tamsulosin HCl product currently available in Australia. However, the clinical efficacy of the two different tamsulosin formulations has been shown to be similar.)

The tamsulosin HCl component of DUTATAM 500/400 consists of a multi-unit pelletised preparation which has modified release properties. The individual pellets consist of a drug core and an outer coating layer which reduces the rate of dissolution of the drug.

The single dose bioequivalence study was performed in both the fasted and fed states. A 30% reduction in C_{max} was observed for the tamsulosin component of dutasteride-tamsulosin in the fed state compared to the fasted state. Food had no effect on AUC of tamsulosin.

Absorption

Dutasteride

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 500 micrograms 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.

Tamsulosin

Tamsulosin hydrochloride is absorbed from the intestine and is almost completely bioavailable. Tamsulosin hydrochloride exhibits linear kinetics, following single and multiple dosing, with achievement of steady state concentrations by the fifth day of once-a-day dosing. The rate of absorption of tamsulosin hydrochloride is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking tamsulosin hydrochloride approximately 30 minutes after the same meal each day.

As noted above, there are differences in the pharmacokinetics of dutasteride 500 microgram and tamsulosin hydrochloride 400 microgram modified release capsule and the current Australian tamsulosin formulation. The following table has been taken from published literature:

	Tamsulosin MR 400 microgram* (n=12) Mean (range)	Tamsulosin OCAS 400 microgram** (n=12) Mean (range)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	277.0 (105 – 559)	201.6 (95 – 470)
t_{max} (h)	6.67 (5.0 - 9.0)	8.51 (3.0 – 24.0)
C_{max} (ng/mL)	13.74 (6.3 – 26.5)	5.88 (3.5 – 12.2)

*This formulation has been shown to be bioequivalent to the tamsulosin in dutasteride 500 microgram and tamsulosin hydrochloride 400 microgram modified release capsule (fed state results)

** Similar to the Tamsulosin formulation currently available in Australia. There are no data which directly compare the bioavailability of the tamsulosin component of dutasteride 500 microgram and tamsulosin hydrochloride 400 microgram modified release capsule with the tamsulosin monotherapy formulation currently available in Australia.

*** This table is comparing pharmacokinetic parameters only and no efficacy differences may be inferred from this table.

Distribution

Dutasteride

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 (greater than 99.5%).

Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after one month and approximately 90% after three months. Steady state serum concentrations (C_{SS}) of approximately 40 ng/mL are achieved after six months of dosing 500 micrograms once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at six 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%.

Tamsulosin

The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to ten healthy male adults was 16 L, which is suggestive of distribution into extracellular fluids in the body.

Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL).

Metabolism

Dutasteride

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.

Tamsulosin

There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolised by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. In vitro results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolizing enzymes may lead to increased exposure to tamsulosin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Excretion

Dutasteride

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 500 micrograms/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 low serum concentrations (less than 3 ng/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 ng/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, the terminal half-life of dutasteride is 3 to 5 weeks, and following repeat dosing of 500 micrograms/day, the slower clearance dominates and the total clearance is linear and concentration-independent. Serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Tamsulosin

Tamsulosin half-life is 5 to 7 hours following intravenous administration. Following the administration of dutasteride 500 microgram and tamsulosin hydrochloride 400 microgram modified release capsule, the tamsulosin half-life was reported to be 12 to 14 hours. Approximately 10% is excreted unchanged in urine.

Special Populations:

No pharmacokinetic studies have been conducted on special patient populations for dutasteride-tamsulosin. The following statements reflect the information available on the individual components.

Elderly

Dutasteride

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.

Tamsulosin

Cross-study comparison of tamsulosin hydrochloride overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in elderly males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal Impairment

Dutasteride

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 500 micrograms dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CL_{cr} < 70$ mL/min/1.73m^2) or moderate-severe ($10 \leq CL_{cr} < 30$ mL/min/1.73m^2) renal impairment and 6 normal subjects ($CL_{cr} > 90$ mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with end stage renal disease ($CL_{cr} <10$ mL/min/1.73m^2) have not been studied.

Hepatic impairment

Dutasteride

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

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

Children

DUTATAM 500/400 is contraindicated for use in children.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Dutasteride and tamsulosin hydrochloride showed no evidence of genotoxicity in a wide range of *in vitro* and *in vivo* tests.

Carcinogenicity

Dutasteride

In a carcinogenicity study in rats, dutasteride produced 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.

Tamsulosin

Oral (dietary) administration of tamsulosin for up to 2 years in rats and mice was associated with an increased incidence of pituitary adenoma, mammary gland hyperplasia, mammary gland fibroadenoma and (in mice only) mammary gland adenocarcinoma. These effects occurred at plasma tamsulosin concentrations (AUC) up to 10 times lower than those expected in men undergoing treatment with tamsulosin, but they were observed only in female animals and are probably due to the hyperprolactinaemic effect of tamsulosin. It is not known if tamsulosin elevates prolactin during prolonged administration in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in female rodents is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

DUTATAM 500/400 capsules also contain the inactive ingredients butylated hydroxytoluene, glyceryl caprylate, gelatin, glycerol, titanium dioxide, microcrystalline cellulose, methacrylic acid - ethyl acrylate copolymer (1:1), talc, triacetin, iron oxide yellow, hypromellose, carrageenan, potassium acetate, TekPrint SW-9008 Black Ink (ID: 2328).

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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

DUTATAM 500/400 capsules are available in HDPE bottle with a polypropylene child-resistant closure in a pack size containing 30 capsules.

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

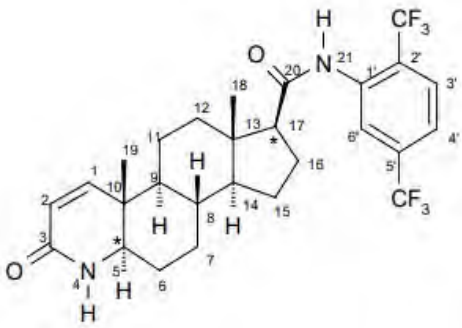
Dutasteride - Dutasteride is a white to pale yellow powder. It is practically insoluble in water, and soluble in organic solvents, dimethyl sulfoxide, acetone, methanol, ethanol and ispropanol.

Tamsulosin Hydrochloride - White or almost white crystalline powder. It is sparingly soluble in water, and slightly soluble in the following solvents; Acetone, Ethanol, Ethyl acetate and Methanol.

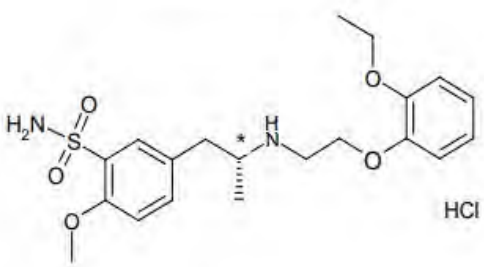
Chemical structure

The pKa values for tamsulosin are as follows: pKa1 = 8.4 (secondary amine) and pKa2 = 10.7 (sulphonamide). The partition coefficient is clogP = 2.2 (calculated using Property Calculator 4.7)

Dutasteride:



Tamsulosin hydrochloride:



Dutasteride:

Chemical Name:
N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide

Molecular Formula: $C_{27}H_{30}F_6N_2O_2$

Tamsulosin hydrochloride:

Chemical Name:
(-)-(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2- methoxybenzenesulfonamide, monohydrochloride

Molecular Formula: $C_{20}H_{28}N_2O_5S \cdot HCl$

CAS number

Dutasteride: 164656-23-9

Tamsulosin hydrochloride: 106463-17-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

MedTAS Pty Ltd
5B 9-13 Redmyre Road
Strathfield
Sydney NSW 2135
Australia
Email: mohit.gupta@medtas.com.au

9 DATE OF FIRST APPROVAL

24/06/2024

10 DATE OF REVISION

26/09/2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8.	Sponsor details update.