



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dutasteride/Tamsulosin

Proprietary Product Name: Duodart

Sponsor: GlaxoSmithKline Australia Pty Ltd

January 2011

TGA Health Safety
Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	New fixed dose combination
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	20 October 2010
<i>Active ingredient(s):</i>	Dutasteride and tamsulosin (as the hydrochloride)
<i>Product Name(s):</i>	Duodart
<i>Sponsor's Name and Address:</i>	GlaxoSmithKline Australia Pty Ltd PO Box 18095 Melbourne Vic 3067
<i>Dose form(s):</i>	Capsules – hard
<i>Strength(s):</i>	400 µg of dutasteride and 500 µg of tamsulosin hydrochloride
<i>Container(s):</i>	HDPE Bottles with Child-Resistant Closures
<i>Pack size(s):</i>	Packs of 7, 30 and 90
<i>Approved Therapeutic use:</i>	Duodart is indicated for the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH).
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	The recommended dose of Duodart is one capsule (500 µg dutasteride /400 µg tamsulosin) taken orally approximately 30 minutes after the same meal each day.
<i>ARTG Number:</i>	162530

Product Background

Benign prostatic hyperplasia (BPH) is a chronic and progressive disease, and is the most common benign neoplasm in ageing males. Pathological changes were found in 88% of men ≥ 80 years, and symptoms have been reported in nearly 50% of men over 50 years of age.¹ The cause of BPH is age related prostate growth which is stimulated by dihydrotestosterone (DHT), which is formed from testosterone by the action of 5 α -reductase isoenzymes type 1 and 2. This prostatic growth may eventually lead to urethral obstruction, causing lower urinary tract symptoms (LUTS), including both voiding symptoms (for example, hesitancy, weak stream, terminal dribbling) and storage symptoms (urgency, frequency, nocturia).

The progressive nature of the disease leads to increased need for surgery and episodes of acute urinary retention (AUR).² There are two components that lead to symptoms. There is a static component that is attributed to the increased pressure in the prostatic urethra secondary to obstruction caused by hyperplasia of the prostatic tissue. There is also a dynamic

¹ Napalkov P, Maisonneuve P, Boyle P. Worldwide patterns of prevalence and mortality from benign prostatic hyperplasia. *Urology* 1995; 46: 41-46.

² McConnell JD, Bruskewitz R, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Eng J Med* 1998; 338: 557-563.

component which is influenced by the adrenergic tone of the prostatic stromal smooth muscle and bladder neck.

The aim of therapy is to improve symptoms and quality of life, and also to prevent complications such as AUR and upper urinary tract dilatation. Current treatment modalities include pharmacotherapy, minimally invasive therapy and conventional surgical therapy.^{3,4}

Current pharmacological treatments recommended by guidelines include alpha-blockers and 5 α -reductase inhibitors (5ARIs). Alpha blockers target the dynamic component of the disease by inhibiting alpha-1 adrenergic receptors in the prostate smooth muscle and bladder neck, thereby relaxing constriction around the prostatic urethra. This leads to improvement in LUTS and the onset is relatively rapid, usually within 2-4 weeks.^{5,6} Alpha blockers can therefore provide rapid relief of symptoms, but have not been shown to delay disease progression.

5ARIs inhibit the conversion of testosterone to DHT, which is the primary stimulator of prostate growth. Lowering DHT leads to reduction of prostate volume, leading to improvement in symptoms, improvement in urinary flow, reduction in the risk of longer term complications such as AUR, and reduction in need for BPH related surgery.⁷ Dutasteride is a potent and selective inhibitor of type 1 and type 2 5 α -reductase isoenzymes, and has been shown to reduce intraprostate and serum DHT by up to 90% within 2 weeks. However, it may take up to 6 months for improvement in symptoms to be noted.⁸

Therefore combining an alpha blocker with a 5ARI is considered an option for providing early onset of symptom relief and prolonged clinical benefit. The combination of an 5ARI (finasteride) and an alpha blocker (doxazosin) over 4 years has been shown in a double blind placebo controlled study to improve symptoms and reduce risk of overall progression significantly more than placebo or either drug alone, in men with mild to severe BPH.⁹ Similarly, co-administration of dutasteride 500 μ g and tamsulosin 400 μ g has been shown to provide a greater degree of symptom improvement compared with either monotherapy over 1-year and 2-year periods.¹⁰ The Current European Association of Urology (EAU) guidance states "Recommendation: The combination therapy with 5ARIs and alpha-blockers seems to be more beneficial and durable than monotherapy by either one of these drugs".¹¹

³ 'Minimally invasive therapy' refers to laser therapy, transurethral needle ablation of the prostate (TUNA), transurethral electrovaporization of the prostate, hyperthermia, high intensity focused ultrasound (HIFU), intraurethral stents and transurethral balloon dilatation of the prostate.

⁴ 'Conventional surgical therapy' refers to transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP) and open simple prostatectomy.

⁵ Beduschi M, Beduschi R, Oesterling JE. Alpha-blockade therapy for benign prostatic hyperplasia: from a nonselective to a more selective alpha_{1A}-adrenergic antagonist. *Urology* 1998; 51: 861-872.

⁶ Clifford GM, Farmer RDT. Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol* 2000; 38: 2-19.

⁷ Kirby R, Fitzpatrick J, Kirby M, Fitzpatrick A. Development of prostatic disease. In: *Shared care for prostatic disease*. Isis Medical Media 1994: 21-35.

⁸ Avodart (dutasteride): Summary of Product Characteristics, 2008.

⁹ McConnel JD, Roehrborn CG, Bautista OM et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Eng J Med* 2004; 340: 2387-2398.

¹⁰ Roehrborn CG, Saimi P, Barkin J et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *Urology* 2008; 179: 616-621.

¹¹ Maderbacher S, Allivizatos G, Nordling J et al. EAU 2004 Guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004; 46: 547-554.

The drug related symptom relief obtained from 5ARIs takes longer to be perceived by the patient than that which is attainable with an alpha-blocker. Therefore there is a possibility that patients may not persist with a 5ARI for long enough to obtain the benefits of longer term delay of disease progression. Combining dutasteride with an alpha-blocker does not only provide the additive benefit of the two drugs, but could ensure that the patient associates both medications with early symptomatic relief, and would therefore persevere with treatment for sufficient time for the 5ARI to modify the underlying condition and reduce risk of disease progression. The use of a single dutasteride-tamsulosin combination (DTC) capsule may encourage early introduction of a 5ARI to therapy whilst also obtaining the symptomatic benefits of alpha-blocker therapy.

Ageing men with BPH have a high prevalence of co-morbidities, and a high proportion, up to 37%, have multiple comorbidities.¹² These comorbidities are generally representative of an ageing male population, and common conditions include hypertension, coronary artery disease, diabetes, malignancy, stroke and congestive cardiac failure.¹² These conditions therefore are likely to require multiple medications, which in addition to two medications for the treatment of BPH, leads to increased polypharmacy.

Non-compliance with medication is a common problem, and elderly patients with multiple comorbidities potentially face many barriers to compliance. These may include confusion, reduced dexterity, and increased number of concurrent medications.¹³ Therefore, any potential reduction in pill burden may be beneficial to overall medication compliance. This could be promoted by use of single combination products. This has been demonstrated to improve compliance to therapy compared to concomitant therapy in areas other than BPH, for example, diabetes, asthma and chronic obstructive pulmonary disease.^{14,15,16} Therefore, it is considered by the sponsors that combining dutasteride and tamsulosin (both of which are active medications in the treatment of BPH, with complementary mechanisms of action), may offer a convenient, easy to take, once daily capsule that may improve compliance over co-administration therapy.

The proposed therapeutic indication for Duodart is:

Duodart is indicated for the treatment and prevention of the progression of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate, to reduce prostate size, alleviate symptoms, improve urinary flow and reduce the risk of acute urinary retention (AUR) and the need for BPH related surgery.

The approved indications for dutasteride are:

Treatment of patients with symptomatic benign prostatic hyperplasia (BPH) with an enlarged prostate

¹² Hutchison A, Farmer R, Chapple C et al. Characteristics of patients presenting with LUTS/BPH in six European countries. Eur Urol 2006; 50: 555-562.

¹³ Edwards L, Roden DM. Principle of prescription order writing and patient compliance. In: Gilman AG, ed. Goodman & Gilman's The pharmacological basis of therapeutics. Tenth edition. USA: McGraw-Hill, 2001; 1903-1915.

¹⁴ Melikian C, White TJ, Vanderplas A, Dezii C, Chang E. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002; 24: 460-467.

¹⁵ Holt S, Masoli M, Beasley R. Increasing compliance with inhaled corticosteroids through the use of combination therapy. J Allergy Clin Immunol 2004; 219-220.

¹⁶ Chrischelles E, Gilden D, Kubisiak J, Rubenstein L, Shah H. Delivery of ipratropium and albuterol combination therapy for chronic obstructive pulmonary disease: effectiveness of a two-in-one inhaler versus separate inhalers. Am J Manag Care 2002; 8: 902-911.

The approved indications for tamsulosin are:

For the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

This submission is closely related to another submission, PM-2009-02236-3-3, evaluated by the TGA at the same time, for an extension of indication for the monotherapy Avodart (dutasteride 500 mg) for the latter to be used in combination with an alpha-blocker.¹⁷

Regulatory Status

Similar applications to register Duodart has been approved in the European Union (EU) on 29 March 2010 and in Switzerland on 17 March 2010. Applications have been submitted in the USA and Canada and are still under review.

In the EU, the indications are:

- Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).*
- Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.*

In Switzerland, the indications are:

- Duodart is indicated as combination therapy for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).*
- Duodart reduces the risk of acute urinary retention and the need for surgery in patients with moderate to severe symptoms of BPH.*

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Introduction

The sponsor, GlaxoSmithKline Australia Pty Ltd, is the innovator of the drug substance dutasteride, having registered immediate release soft capsules containing dutasteride 500 mg under the brand name Avodart in November 2002. No generic products containing dutasteride are registered in Australia.

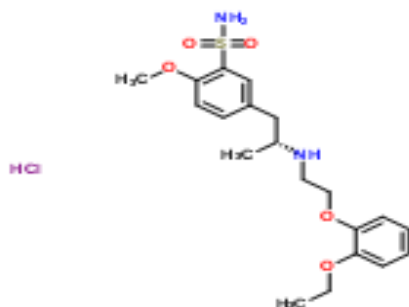
A modified release capsule containing tamsulosin hydrochloride (HCl) 400 µg originally registered in Australia by CSL Ltd (Flomax) for the treatment of benign prostatic hyperplasia is no longer supplied. However, a modified release film-coated tablet containing tamsulosin HCl 400 mg is now registered in Australia by CSL under the brand name Flomaxtra. This is indicated for the 'relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)'. No generic products containing tamsulosin HCl are registered in Australia.

Drug Substance (active ingredient)

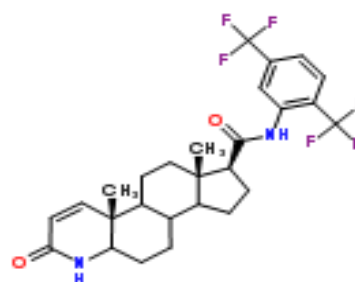
The details relating to dutasteride are the same as for the sponsor's registered monotherapy.

A Drug Master File has been provided for tamsulosin hydrochloride. The drug substances have the following structures:

¹⁷ TGA. AusPAR for Dutasteride (<http://www.tga.gov.au/pmeds/auspar/auspar-duodart.pdf>).



Tamsulosin HCl



Dutasteride

Dutasteride: All details relating to dutasteride drug substance are the same as for the Avodart capsules. Dutasteride is practically insoluble in water and buffers including simulated gastric fluid and simulated intestinal fluid, but is fully dissolved in the 'mono- and di-glycerides' (MDC) excipient during manufacture of the intermediate soft gelatin capsule. Consequently, controls over the particle size distribution and morphology are unnecessary for this ingredient.

Tamsulosin HCl: A Drug Master File was submitted for the synthesis of this active by a single manufacturer at two alternative sites. An acceptable specification was provided that includes adequate controls over particle size distribution, residual solvents and enantiomeric purity. Polymorphism has not been reported for this active.

Drug Product

Formulation(s)

The finished product is an outer hard capsule which contains both an immediate release soft capsule containing dutasteride 500 mg, and modified release pellets containing tamsulosin HCl 400 mg (total). The tamsulosin HCl pellet coating acts as an enteric coat and the core gives sustained release at higher pH. Tamsulosin HCl will be referred to as tamsulosin for the remainder of this AusPAR

Manufacture

The intermediate tamsulosin pellets are manufactured by Rottendorf Pharma GmbH in Germany, whilst the immediate release soft capsules containing dutasteride are manufactured by Catalent France Beinheim SA in France. Manufacture, quality control testing, packaging and labelling and release for supply of the finished product is performed by Catalent Germany Schorndorf GmbH in Germany.

The composition of the contents of the immediate release dutasteride soft gelatin capsules used in this product is qualitatively identical but quantitatively different to that of the registered Avodart soft gelatin capsules, and the capsule shell is also different. However, the method of manufacture is identical, involving heating the MDC to dissolve the dutasteride and butyl-hydroxytoluene, followed by filling the soft gelatin capsules (prepared *in situ*) using a rotary die process, before drying and bulk packaging.

Manufacture of the intermediate tamsulosin pellets involves sequential granulation, extrusion/spheronisation, drying, enteric-coating, drying, sieving, blending and bulk packaging.

The final finished hard hypromellose capsules are first filled with the intermediate tamsulosin modified release pellets, the immediate release dutasteride soft gelatin capsules are then added and the capsules closed, weight sorted and bulk packaged (aluminium foil pouches).

Final packaging is in a HDPE bottle with child-resistant closure and a foil induction-seal liner.

Of the finished product excipients, only the gelatin used in the immediate release dutasteride capsules is of animal origin. The pathogen safety of this excipient has been evaluated by the Office of Devices Blood and Tissues and found acceptable.

Specifications

Generally, the release and expiry limits applied to the finished product are appropriate, and allow for any changes observed on storage

Stability

Stability data have been generated under stressed, accelerated and real time conditions to characterise the stability profile of the product. These do not support the shelf life originally proposed (2 years stored below 25°C), but do support a shelf life of 2 years stored below 25°C, which has been accepted by the sponsor.

Biopharmaceutics

The submission included six studies, two of which have been evaluated. The submission included justifications for not performing a bioequivalence study comparing the hard capsules to the tamsulosin tablets registered in Australia. This only included clinical argument, which was referred to the Delegate.

The pivotal Phase III efficacy studies were performed with Avodart 500 µg dutasteride soft capsules and 400 µg tamsulosin modified release capsules (Flomax sourced from the US and Omnic MR sourced from Germany).

Six bioavailability studies were provided. The sponsor also referred to an interaction study previously evaluated. Each of the two studies evaluated used an appropriate study design and appropriately validated test methods for the determination of dutasteride and tamsulosin.

ARI109882: This was an open-label, randomized, single-dose, three-period, partial crossover study that compared the proposed Duodart 500µg/400µg fixed-dose combination capsule to concomitant dosing with Avodart and US Flomax in both fed and fasted states. From the results of this study, it was shown that:

- The dutasteride and tamsulosin responses from the proposed capsules are bioequivalent (the maximal plasma concentration [C_{max}] and the area under the plasma concentration time curve [AUC]) to the responses from the monotherapies used in the Phase III efficacy studies in both the fasted and fed states.
- Food does not affect the bioavailability (C_{max} and AUC) of dutasteride from the proposed capsules.
- Food does not affect the extent of bioavailability (AUC) of tamsulosin from the proposed capsules, but it lowers the rate of bioavailability (C_{max}) of tamsulosin by 30%.
- Food delayed the time to maximal plasma concentration [T_{max}] for both actives by ~1 hour, irrespective of formulation.

When adjusted for the assayed content of each active, the outcomes (below) were unchanged.

ARI111402: This was an open-label, randomized, repeat dose, 3 period crossover steady state study that compared the proposed Duodart 500µg/400µg capsule (and another developmental fixed-dose combination product containing tamsulosin pellets with a 15% w/w coat instead of the 10% w/w coat proposed for Australia) to concomitant dosing with Avodart and US Flomax in the fasted state, from the results of which it was shown that:

- The tamsulosin response from the proposed capsules is bioequivalent (C_{\max} and AUC) to the response from the monotherapies used in the Phase III efficacy studies in the fasted state after a repeat dose.
- The tamsulosin response from the 15% coating capsules is also bioequivalent (C_{\max} and AUC) to the response from the monotherapies used in the Phase III efficacy studies in the fasted state after a repeat dose, but in this case the response was ~10% lower.

Four other studies (ARI10021, ARI103880, 163/07, 186/07) were not evaluated by the quality evaluator but are described in the clinical section (see *Section IV*). However, in each case the formulations were shown to be bioequivalent.

There was also a single dose study (ARIA1011) that assessed the pharmacokinetic (PK) interaction between dutasteride and tamsulosin (and terazosin) in 48 subjects which is discussed in *Section IV*.

Justifications Submitted For Non-Supply of Bioavailability/Bioequivalence Data

The submission did not include results from a study to investigate any potential pharmacokinetic interaction of tamsulosin with dutasteride. Instead, the sponsor put forward clinical arguments as to why such an interaction is unlikely, and these were referred to the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) for comment.

No data on the absolute bioavailability of the capsules were provided, but given the results of the six studies above, it was accepted on a risk management basis that results for the proposed Duodart 500µg/400µg capsule are similar to those for the relevant monotherapy products.

No bioavailability data were provided comparing the proposed product to formulations available in Australia (important if patients are to switch products). The draft PI does not specifically contraindicate Australian patients being switched from the registered Avodart soft gelatin capsules or the registered FlomaxTRA modified release tablets or a concomitant combination of these products to the proposed Duodart 500µg/400µg hard hypromellose capsules. The Avodart product used in the Phase III efficacy and bioavailability studies is identical to that registered in Australia. However no bioavailability data were generated using the registered FlomaxTRA modified release tablets. A justification for this has been provided. This is based on published papers that show the following:

- The clinical effect and safety of a *tamsulosin oral controlled absorption system* (“tamsulosin OCAS”) tablet are similar to the clinical effect and safety of a tamsulosin modified release pellet-containing capsule (tamsulosin MR) even though they are not bioequivalent.
- This justification assumes that the tamsulosin OCAS tablets referred to in the papers are those registered for supply in Australia and the tamsulosin MR capsules are those that were previously registered in Australia. The sponsor has not and is unable to demonstrate this is the case.
- In relation to bioequivalence, one paper indicated that:¹⁸
 - o After administration of a single dose of 400 mg in the fasted state, AUC results from the tamsulosin OCAS tablet were 30% lower than from the tamsulosin MR capsule and had C_{\max} results 60% lower. Thus, the tamsulosin OCAS tablet gives a more constant response and possibly lower adverse events. A corollary to this might be that the proposed product (which uses pellets) is likely to give a less constant

¹⁸ Martin MC et al, European Urology Supplements 2005; 4: 15-24.

response and possibly higher adverse events compared to the registered FlomaxTRA modified release tablets.

- In a multiple dose study the tamsulosin OCAS tablet reached steady state in 3 days, had a linear response over 400 - 1200 mg and was not affected by food.

During the course of evaluation of this submission, the sponsor was requested to provide any other comments relevant to the evaluation of the bioavailability data and the justification for not providing bioavailability data, and the sponsor's response was initially found to be unacceptable following its referral for clinical comment. The comparison of the pharmacokinetic parameters from the tamsulosin OCAS tablet and a tamsulosin modified release capsule indicates that C_{max} from the latter is over double that obtained from the OCAS tablet, and no comparison of AUC was made.

Consideration by PSC

Details of this submission were presented at the 132nd meeting of the Pharmaceutical Subcommittee (PSC) of the ACPM in May 2010. The PSC had reservations regarding:

- Safety aspects of the proposed tradename.
- The large difference in the elimination half-lives of dutasteride and tamsulosin.

These issues remain unresolved.

The PSC also made some comments on information contained in the draft PI and Consumer Medicine Information (CMI), which were resolved to the satisfaction of the TGA.

Quality Summary and Conclusions

The administrative, quality, pathogen safety, microbiological and biopharmaceutic data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

A number of deficiencies and other issues requiring resolution before the product could be recommended for approval were identified during the evaluation and were referred to the sponsor for comment or resolution. Most were resolved.

Although the sponsor has not yet satisfactorily addressed all issues raised, the following recommendations can be made:

1. A shelf life of 2 years stored below 25°C can be allocated to the capsules packaged in the HDPE bottles proposed for Australia.
2. Subject to the satisfactory resolution of the matters taken up with the sponsor, approval is conditionally recommended from a quality perspective. The condition of approval is that a release and expiry *Dissolution (% tamsulosin HCl released)* test limit of "48% - 68% LC released after 3 hours" will be applied to the finished product.
3. The pivotal clinical studies have shown that:
 - The dutasteride and tamsulosin responses from the proposed capsules are bioequivalent (C_{max} and AUC) to the responses from the US monotherapies used in the Phase III efficacy studies in both the fasted and fed states (single dose).
 - Food does not affect the bioavailability (C_{max} and AUC) of dutasteride from the proposed capsules.
 - Food does not affect the extent of bioavailability (AUC) of tamsulosin from the proposed capsules, but it lowers the rate of bioavailability (C_{max}) of tamsulosin by 30%.

- Food delayed T_{\max} for both actives by ~1 hour, irrespective of formulation.
- The tamsulosin response from the proposed capsules (10% coating) is also bioequivalent (C_{\max} and AUC) to the response from the monotherapies used in the Phase III efficacy studies in the fasted state after a repeat dose.
- The tamsulosin response from the developmental formulation with 15% coating is also bioequivalent (C_{\max} and AUC) to the response from the monotherapies used in the Phase III efficacy studies in the fasted state after a repeat dose, but in this case the response was ~10% lower.

The sponsor has confirmed that the Avodart product used in the Phase III studies is identical to that registered in Australia, and has provided justifications for not providing biopharmaceutic data comparing the proposed capsule with the Australian registered formulation of tamsulosin HCl. There was no pharmaceutical chemistry aspect to the sponsor's justification, which was referred for clinical assessment.

4. The potential for dose-dumping of the tamsulosin if large quantities of ethanol are imbibed prior to the meal consumed before administration of the Duodart capsule was also drawn to the attention of the ACPM.

III. Nonclinical Findings

Introduction

The sponsor sought approval for a fixed dose combination of dutasteride (500µg) and tamsulosin (400 mg) to be taken orally for the treatment of benign prostatic hyperplasia (BPH) and acute urinary retention (AUR).

No nonclinical studies were submitted that used a combination of dutasteride and an alpha blocker. The sponsor justified the absence of these studies by reference to the TGA-adopted European Medicines Agency (EMA) guideline and consideration of the following factors:¹⁹

- Extensive clinical experience; and
- The absence of nonclinical signals that indicate the potential for additive or synergistic toxicity.

The sponsor has previously provided a justification for the absence of combination studies to EU regulatory agencies and it was agreed that additional nonclinical studies were not warranted. One of the EU agencies noted that the age of the tamsulosin data package (many studies pre-1990) meant that many parts of the nonclinical data package were not in accordance with modern standards. It was suggested that any gaps in such data that were not superseded by clinical data should be updated according to scientific and regulatory developments since the time of the original submission.

Comprehensive reviews of the pharmacology, pharmacokinetic and toxicology of dutasteride and tamsulosin have previously been conducted by the TGA and other international regulatory agencies.

Dutasteride has been reviewed by the TGA in the original marketing application for Avodart and a subsequent application for co-administration of dutasteride and tamsulosin (2009-02236-3-3).¹⁷ The only new data in the current submission for dutasteride were limited to a secondary pharmacology study, three method validation studies and five pharmacokinetic studies.

¹⁹ EMEA, Committee for Medicinal Products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products, CHMP/SWP/258498/2005.

Tamsulosin has been reviewed by the TGA in the original marketing application for Flomax/Omnice and also a subsequent application referred to above. In this submission the sponsor has mainly relied on the FDA Approval package for Flomax available in the public domain but has also supplemented this with some scientific literature. The only new data submitted for tamsulosin consisted of two secondary pharmacology studies, a safety pharmacology study, two pharmacokinetic studies and four method validation studies.

The assessment below integrates this new data into an overall discussion of the potential for dutasteride and tamsulosin in combination to elicit adverse pharmacodynamic, pharmacokinetic and toxicological interactions.

Pharmacology

Potential pharmacodynamic interactions

New studies in this submission (*in vitro* competitive binding assays and functional assays using cell lines) showed that dutasteride had little affinity for a wide range of other steroid receptors (androgen, oestrogen, glucocorticoid, mineralocorticoid, progesterone) up to a maximum concentration of 30 μM , and it showed no agonist or antagonist activity at the tested receptors up to a maximum concentration of 10 μM .

New data from the testing of tamsulosin activity towards a large panel of 7-transmembrane monoamine receptors showed that (relative to its affinity for the human alpha-1A adrenergic receptor) tamsulosin had moderate affinity for the alpha-1B and -1D adrenergic receptors, and weak affinity for the dopamine D₃ and serotonin 5-HT_{1A} receptors (Table 1). All other receptors examined showed negligible affinity. For example, the alpha-2A and -2B adrenergic receptors showed 6,000-fold lower affinity. These results support the selectivity of tamsulosin for alpha-1A adrenergic receptors.

Table 1: Tamsulosin selectivity (agonist or antagonist assay) towards selected 7-transmembrane receptors

Receptor	Fold selectivity (relative to alpha-1A)
alpha-1A adrenergic receptor	-
alpha-1B adrenergic receptor	<10
alpha-1D adrenergic receptor	<10
dopamine D ₃ receptor	10-100
serotonin 5-HT _{1A} receptor	10-100
alpha-2A adrenergic receptor	6,000
alpha-2B adrenergic receptor	6,000

The potential for pharmacodynamic interactions on the cardiovascular system between tamsulosin and dutasteride appears to be low. Alpha blockers such as tamsulosin cause well known dose-dependent decreases in blood pressure in experimental animals and humans while dutasteride had little effect on major cardiovascular parameters (including electrocardiogram [ECG]) in dogs at C_{max} levels of 15 to 30 times that anticipated in humans at the maximum recommended human dose (MRHD).

Newly submitted data for tamsulosin showed a hERG channel median inhibitory concentration [IC₅₀] of 105 μM , a value that is about 3,000-times the C_{max} for tamsulosin after a 400 mg clinical dose (based on a C_{max} value of around 16 ng/mL; study ARI111402). When this result is taken together with the observation that dutasteride tends to shorten,

rather than prolong action potentials (isolated dog Purkinje fibres), the potential for the combination to cause QT prolongation is considered to be very low.

Clinical studies with the dutasteride/tamsulosin combination have shown no increase in postural hypotension, no QT prolongation, and no effect of tamsulosin on dutasteride's suppression of DHT levels (sponsor's *Nonclinical Overview*).

Overall, direct pharmacodynamic drug interactions between dutasteride and tamsulosin are unlikely due to their fundamentally different mechanisms of action which occur at different, highly specific, target sites: dutasteride inhibits SRD5A2 activity (and hence DHT-induced hyperplasia) in prostatic glandular tissue while tamsulosin primarily targets alpha-1A adrenergic receptors on prostatic stromal smooth muscle and the bladder neck, thus relaxing the constriction of the prostatic urethra.

Pharmacokinetics

Potential Pharmacokinetic interactions

Nonclinical pharmacokinetic interaction studies were not performed with dutasteride and tamsulosin. The EU guideline adopted by the TGA notes:²⁰

“Provided that the pharmacokinetics of the single components are adequately characterised in animals, including the profile for enzyme induction and inhibition and drug-drug interactions, additional non-clinical documentation on pharmacokinetic interactions is generally not needed.”

Protein binding for dutasteride was high (>99.5%) across all species tested, including humans while that for tamsulosin was moderately high (80-82% in rats, 90 to 93% in dogs and 94-99% in humans). *In vitro* studies showed that:

- 1) dutasteride neither displaced nor was displaced from human serum proteins by warfarin, diazepam or phenytoin, or by acenocoumarol or phenprocoumon; and
- 2) tamsulosin neither displaced nor was displaced from human serum proteins by amitriptyline, diclofenac, glyburide, simvastatin plus metabolite, warfarin, diazepam, propranolol, trichlormethiazide or chlormadinone.

New data in this submission showed that the passive cellular membrane permeability coefficient of dutasteride, in the presence of a P-glycoprotein (Pgp) inhibitor, was 78 nm/s, indicating moderate permeability. However, this value was reduced to only 10 nm/s in the presence of apical fasted state simulated intestinal fluid, perhaps reflecting the effects of micellar solubilisation by bile. By comparison, amprenavir (a high permeability drug) had a value of 289 nm/s.

Previous applications have shown that dutasteride undergoes oxidative metabolism to various hydroxylated metabolites by cytochrome P450 (CYP)3A4 and CYP3A5 and is also metabolised by SRD5A1 and SRD5A2 to generate the metabolite 1,2-dihydrodutasteride. New data in this submission investigated the ability of dutasteride to inhibit the functioning of a variety of proteins involved in drug metabolism and transport. The proteins examined included CYP enzymes, organic anion transporters (OAT1, OAT3, OATP1B1, and OATP1B3), multidrug resistance proteins (MRP2), and a protein that upregulates CYP3A4 gene in response to various toxic substances (pregnane X receptor (PXR)). Dutasteride was a very weak inhibitor of most of these proteins (Table 2). Two exceptions were the transporters OAT3 and OATP1B1, which showed IC₅₀ values of around 1 µM. Given that the serum

²⁰ EMEA, Committee for Medicinal Products for Human Use (CHMP), 13 October 2005. Note for Guidance of Fixed Combination Medicinal Products, CPMP/EWP/240/95.

concentration of dutasteride is around 75 nM after one year of clinical treatment and that dutasteride is highly protein bound in serum, interaction of dutasteride with OAT transporters in man should not be of significance.

Table 2: IC₅₀ values for interaction of dutasteride with various drug-processing proteins

Protein	pIC ₅₀
CYP 1A2	< 4
CYP 2C9	< 4
CYP 2C19	4.3
CYP 2D6	< 4
CYP 3A4	< 4 and 4.3
MRP2	< 4
OAT1	< 4
OAT3	6.3 and 5.8
OATP1B1	6.1
OATP1B3	4.2 and 4.7
PXR	< 5

Tamsulosin is extensively metabolised by CYP3A4 and CYP2D6 in the liver. While the effect of tamsulosin on dutasteride pharmacokinetics has not conclusively been demonstrated, terazosin, warfarin, digoxin and cholestyramine did not interact with dutasteride in clinical studies.

Overall, it can be concluded that co-administration of dutasteride and tamsulosin is unlikely to yield clinically significant pharmacokinetic interactions as neither compound has been shown to be an inducer or inhibitor of hepatic metabolising enzymes and clinical data have shown no effect of dutasteride on the steady-state pharmacokinetics of tamsulosin.

Toxicology

Potential toxicological interactions

Nonclinical toxicological interaction studies were not performed with dutasteride and tamsulosin. However, the toxicology of the individual components has been previously well characterised in previous applications and the FDA review of Flomax (Application number 020579).

General toxicity

Dutasteride was relatively well tolerated in the rat (and mouse) toxicity studies, with findings primarily reflecting pharmacological activity (that is, prostate/seminal vesicle atrophy and reduced secretion). Reversible neurological signs indicative of central nervous system (CNS) toxicity (for example, unsteady gait, incoordination, shaking/tremors) were observed at higher doses (10-50 mg/kg/day) in the dog studies of 26 and 53 weeks duration, and to a lesser extent in rats. However, such effects were only evident at relative systemic exposure levels (based on the minimum plasma concentration [C_{trough}]) more than 100 to 200 times that anticipated at the maximum recommended human dose.

The toxicity profile of tamsulosin in animals was typical of that observed with other alpha-1-adrenoceptor antagonists currently registered in Australia. Toxic effects such as decreased

salivation, intermittent tremors, hypoactivity, reduced heart rates, ECG changes and decreases in body weight gain were only seen in dogs at more than 500 times the anticipated human exposure (based on AUC).

Given that signs of overt toxicity were only observed at very high exposure margins for both drugs, the potential for toxicological interactions should be low with combined use.

Genotoxicity and Carcinogenicity

Studies in these categories were not performed with Duodart. Previous submissions demonstrated a lack of evidence, from a wide range of *in vitro* and *in vivo* tests, for induction of genotoxicity by either dutasteride or tamsulosin. It is reasonable to assume that the drug combination will show the same lack of response in these tests as the individual drugs.

Rodent carcinogenicity studies with dutasteride showed an increase in Leydig cell tumours at high relative systemic exposure margins (123-fold at the No Observable Effect Level [NOEL] in mice) which was attributable to chronic stimulation by elevated luteinising hormone (LH) resulting from pharmacological perturbation of the hypothalamic-pituitary-testes axis. This effect has also been seen with finasteride and has been shown to be rodent-specific and therefore not relevant to humans.

Rodent carcinogenicity studies with tamsulosin were complicated by tamsulosin's significant dopamine D2-receptor antagonist effects, with much of the treatment-related pathological changes observed in animals (including increased mammary tumours in female rats and mice) being due to the hyperprolactinaemic activity of the drug. Male animals were much less sensitive to the hyperprolactinaemic effects of tamsulosin than females and it is noted that co-administration of dutasteride and tamsulosin will be contraindicated in women due to the risk of dutasteride exposure to the male fetus (see below).

The overall potential of co-prescribed dutasteride/tamsulosin should be low as the former decreases prostate hypertrophy and is therefore more likely to decrease subsequent carcinogenic activity.

Reproductive Toxicity

Co-administration of dutasteride and an alpha blocker is only indicated for men; women are not included in this indication and the use of this combination is clearly contraindicated for women. Therefore, no combination embryofetal development studies were necessary.

The reversible impairment of male fertility in the rodent by both dutasteride and tamsulosin is consistent with their pharmacological effects. Dutasteride's effect is related to a rodent-specific effect related to the failure to form copulatory plugs and is not relevant to humans. Tamsulosin, like other alpha-1-adrenoceptor antagonists, impairs ejaculation, an effect which has been noted clinically.

Feminisation of male fetuses after treatment of pregnant rats and rabbits with dutasteride was observed in previous studies; an expected response to a SRD5A2 inhibitor. A NOEL was not established in either species and use of dutasteride is contraindicated in pregnancy. Nevertheless, rhesus monkey fetal development was unaffected by low intravenous (IV) maternal doses (about 45-260 ng/kg/day), which were high multiples of likely human female exposure via the semen of treated males.

Tamsulosin, at oral doses causing maternal toxicity, was not embryotoxic or teratogenic when administered during gestation in rats (doses up to 300 mg/kg/day) or rabbits (doses up to 50 mg/kg/day).

Taken together, the results above suggest no additional cause for concern for co-administration outside of the issues that are currently well known for the individual drugs (for example, impairment of ejaculation by an alpha blocker).

Nonclinical Summary and Conclusions

Nonclinical studies using a combination of dutasteride and tamsulosin were not submitted. New data were primarily limited to secondary and safety pharmacology studies with the individual components.

New data showed that dutasteride:

- 1) Has little affinity for a wide range of other steroid receptors (androgen, oestrogen, glucocorticoid, mineralocorticoid, progesterone);
- 2) Has moderate passive cellular membrane permeability; and,
- 3) Is unlikely to have any significant effect on CYP enzymes, organic anion transporters, or multidrug resistance proteins at clinically relevant plasma concentrations.

New data for tamsulosin confirmed its high affinity for the human alpha-1A adrenergic receptor (with moderate affinity for the 1B and 1D sub-types) and showed that it had low affinity for the hERG channel (IC₅₀ of 105 µM; 3,000-times the C_{max} for tamsulosin after a 400 mg clinical dose).

Consistent with the appropriate TGA-adopted guideline, the results support the specificity of dutasteride and tamsulosin, and suggest that the potential for undesirable pharmacodynamic, pharmacokinetic, or toxicological interactions following co-administration is low.

The sponsor provided an acceptable justification for the absence of nonclinical combination studies by reference to the appropriate TGA-adopted guideline and consideration of extensive clinical experience with co-administration of the products. Moreover, the nonclinical profiles of both dutasteride and tamsulosin have been previously reviewed by the TGA and other international regulatory agencies and have been expanded by the new data contained in the current submission.

Overall, the weight of nonclinical evidence suggests that the potential for adverse pharmacodynamic, pharmacokinetic or toxicological interactions with Duodart is low. Therefore, there were no objections, on nonclinical grounds, to the registration of Duodart for the treatment of benign prostatic hyperplasia and acute urinary retention.

IV. Clinical Findings

Introduction

This application sought to register Duodart (dutasteride 500µg-tamsulosin 400µg [DTC]) for the treatment of moderate to severe symptoms of BPH and for the reduction in the risk of AUR and surgery in patients with moderate to severe symptoms of BPH. Support for the role of each of the individual components in the treatment of BPH has been previously established as part of their respective development programs, and is not evaluated in this report.

There were data from six studies relating to the clinical pharmacology of Duodart. There were three Phase III clinical studies to support the efficacy and safety of co-administration of dutasteride and tamsulosin. Study ARI40005 was a pre-determined interim 2-year analysis of a long-term pivotal study. Supporting data was presented in studies ARI40002 and ARI40013 (both studies examined the co-administration of dutasteride and tamsulosin and not the proposed combination capsule).

Data from seven previously submitted clinical trials were also included, but as these had already been evaluated elsewhere, they were not evaluated for this report. These included

three pivotal studies establishing the safety and efficacy of dutasteride monotherapy which led to EU approval of dutasteride, and also published literature establishing the safety and efficacy of tamsulosin monotherapy.

All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained from all subjects and the studies were performed in accordance with the Declaration of Helsinki.

Pharmacodynamics

No new data were provided in the submission.

Pharmacokinetics

Six pharmacokinetic studies examined the bioequivalence of different formulations and under different conditions in 241 healthy male subjects. Bioanalysis of dutasteride and tamsulosin serum concentrations was conducted using a validated analytical method based on protein precipitation followed by HPLC-MS/MS analysis.

Bioequivalence

Food effect

An open-label, randomised, single dose, three-period, partial crossover study (**ARI109882**) examined bioequivalence and food effect of a combination capsule formulation of dutasteride and tamsulosin (500µg /400 mg) compared to concomitant dosing of Avodart 500µg and Flomax 400 mg commercial capsules (tamsulosin) in 101 healthy male subjects, aged 19 to 45 years, in the fasted and the fed state. This study was also evaluated by the quality evaluator (see *Section II*). The four treatment regimens are shown in Table 3.

Table 3: Treatment regimens in ARI109882

Treatment Regimen	Description
A	Flomax 0.4 mg (sustained release capsule commercially available in United States) and AVODART 0.5 mg in a fed state (Reference)
B	Dutasteride and Tamsulosin HCl Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin HCl in a fed state (Test)
C	Flomax 0.4 mg (sustained release capsule commercially available in United States) and AVODART 0.5 mg in a fasted state (Reference)
D	Dutasteride and Tamsulosin HCl Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin HCl in a fasted state (Test)

The median T_{max} values for dutasteride ranged from 2.0 to 4.0 hours for all regimens and mean C_{max} (2.0 ng/mL) and the area under the plasma concentration time curve from time zero to time t ($AUC_{(0-t)}$) values (ranging from 29.2 to 33.3 ng h/mL) were very similar. The point estimates for the comparisons of the dutasteride pharmacokinetics between the treatment groups were all close to unity and the 90% confidence intervals (CIs) were well within the accepted levels (80 - 125 %) of bioequivalence. Therefore, fasting or feeding before administration or dosing in the presence or absence of 400 mg tamsulosin had little effect on the C_{max} and AUC of dutasteride. Dutasteride T_{max} values were also equivalent

between regimens, except for the regimens B-D and A-C where the mean T_{\max} was observed 1 hour later in the fed compared to the fasted state.

The median T_{\max} values for tamsulosin ranged from 5 to 7 hours, and it was eliminated with mean half-life ($t_{1/2}$) values ranging from 11.9 to 13.1 hours for all regimens. Mean C_{\max} values for tamsulosin in all regimens ranged from 9.75 to 14.6 ng/mL, whereas, mean $AUC_{(0-\infty)}$ and the area under the plasma concentration time curve from time zero to infinity (AUC_{∞}) values ranged from 164 to 189 ng h/mL. The 90% CIs associated with the AUC and $t_{1/2}$ values of tamsulosin for the comparisons of all regimens were contained within the 0.8-1.25 equivalence interval. By contrast, the C_{\max} values of tamsulosin for Regimen A and Regimen B were found to be 30% less than Regimen C and Regimen D, respectively, suggesting that food affected both the test and reference dosage forms in a similar way and this was reflected in the 90 % CIs for the A:C and B:D comparisons being below the level of equivalence. The 90% CIs for tamsulosin T_{\max} values included 0 in almost all cases, indicating that there was no significant difference between regimens, however, for the Regimen A-C comparisons, a 1.50 hour increase in T_{\max} was observed.

Bioequivalence was established between combination tablet (Duodart) and co-administration of dutasteride and tamsulosin with regard to both dutasteride and tamsulosin pharmacokinetics as the ratios for A:B and C:D was close to unity.

Effect of enteric coating

An open-label, randomised, repeat dose, 3 period crossover study (**ARI111402**) examined the bioequivalence of 3 different formulations of tamsulosin co-administered with dutasteride at steady state in 24 healthy male subjects, aged 19 to 45 years, under fasted conditions. Twenty three subjects completed the study. However it was not clearly stated which of these formulations was the one proposed for marketing. This study was also evaluated by the quality evaluator (see *Section II*).

Each subject received one of the three treatment regimens in each dosing session. Subjects were randomised to one of 6 treatment sequences ABC, ACB, BAC, BCA, CAB, or CBA.

Regimen	Description
A	Dutasteride and Tamsulosin Hydrochloride Combination Capsule, 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride (test)
B	Dutasteride and Tamsulosin Hydrochloride Combination Capsule, 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride (test)
C	Flomax 0.4 mg (sustained release capsule commercially available in United States) and AVODART 0.5 mg (reference)

The median T_{\max} value of tamsulosin following once daily oral administration of regimens A, B and C was 5.0 hours on both Days 1 and 7. AUC_{0-24} and C_{\max} ranged from 132 to 181 ng.h/mL and 13.6 to 16.9 ng/mL, respectively. Tamsulosin was eliminated slowly with mean $t_{1/2}$ values ranging from 13.7 to 14.1 hours on Day 7. Following once daily oral administrations of regimens A, B and C for 7 days, the plasma concentration at the end of the dosing interval (C_{τ}) ranged from 2.22 to 3.34 ng/mL.

Regimens A and C were bioequivalent as the point estimates for the 90% CIs of $AUC_{(0-24)}$, C_{\max} , C_{τ} , C_{trough} and $t_{1/2}$ were contained within 0.80 to 1.25 interval. Similarly, for regimens B and C the point estimates of $AUC_{(0-24)}$, C_{\max} , C_{trough} , C_{τ} and $t_{1/2}$ were contained within the 0.80 to 1.25 interval, suggesting that there was no significant difference in the pharmacokinetics of tamsulosin under the two conditions. For T_{\max} the 90% CIs estimates included zero, indicating that there was no significant difference in the T_{\max} of tamsulosin between regimens A and B versus regimen C.

The point estimates of slope (versus day) and corresponding 90% CIs for tamsulosin C_{τ} values in regimens A, B and C were 1.00 (0.96, 1.04), 0.96 (0.92, 1.00), and 0.98 (0.93, 1.04), respectively. The 90% CIs were all within (0.91, 1.10), indicating that the steady state was achieved for all regimens. Although no direct comparison was made between the A and B formulations (10% and 15% enteric coated, respectively) it would appear that both the A and B formulations are bioequivalent with the combination treatment of the commercially available tablets (formulation C). The effect of the different formulations on dutasteride pharmacokinetics was not examined in this study.

Effect of Capmul

Capmul MCM (glyceryl mono- and di-caprate) is an emulsifying agent used in the production of the capsules. An open label, single dose, randomised, three period crossover study (**ARI103880**) investigated the relative bioavailability of dutasteride 500µg from soft gelatin capsules containing 350 mg of Capmul MCM (Avodart - reference) (Treatment A) versus soft gelatin capsules containing 300 mg (Treatment B) and 100 mg of Capmul MCM (Treatment C) in 37 healthy male volunteers, aged 19 to 48 years.

The mean the area under the plasma concentration time curve from time zero to 72 hours ($AUC_{(0-72)}$), C_{\max} and T_{\max} for dutasteride for the three formulations were similar and ranged from 23.5 to 26.3 ng.hr/mL, 2.15 to 2.48 ng/mL and 1 - 2 hours, respectively.

For the comparison of treatment B versus treatment A, the least squares (LS) means ratios for C_{\max} and AUC were 0.90 and 0.95 respectively and the 90% confidence intervals fell within the level of bioequivalence (0.80 - 1.25). For the comparison of treatment C versus treatment A the LS means ratios for C_{\max} and AUC were 0.87 and 0.93 and although the 90% CI for AUC was within the level of bioequivalence the 90% CI for C_{\max} (0.79 to 0.96) suggested that treatments A and C although similar were not strictly bioequivalent and the amount of emulsifying agent (Capmul) contained in the formulation had an effect on dutasteride C_{\max} with slightly lesser C_{\max} in test formulation Capmul compared to standard soft gelatine capsules.

Tamsulosin from two sources

A randomised, two-period, cross-over, bioequivalence study (**163/07 Sython Pilot I**) compared tamsulosin 400 mg MR (modified release) capsules (test product - Sython BV, The Netherlands) to Flomax 400 mg MR capsules (reference product - Boehringer Ingelheim Pharmaceuticals, Inc, USA) in 26 healthy subjects, aged 19 to 47 years, under fed conditions.

The AUC_{0-t} , AUC_{∞} and C_{\max} for the reference and test formulations were similar and the ratios for the comparison of test versus reference treatment for the three pharmacokinetic parameters ranged from 0.99 to 1.04. In addition, the 90% CIs for the comparisons of the PK parameters (ranged from 0.93 to 1.12) fell within the level of bioequivalence.

A single centre, randomised, single dose, laboratory-blinded,²¹ 2-period, 2-sequence, crossover study (**186/07 Sython Pilot II**) compared the relative bioavailability of two different formulations of tamsulosin in 26 healthy male subjects, aged 21 to 56 years, under fed conditions. The test product used was tamsulosin 400 mg and the reference product was Flomax 400 mg.

The AUC_{0-t} , AUC_{∞} and C_{\max} for the reference and test formulations were similar and the ratios for the comparison of test versus reference treatment for the 3 pharmacokinetic parameters ranged from (0.99 to 1.05). The 90% CIs for the test to reference ratios of the

²¹ The randomisation code was not available to the personnel in charge of the determination of plasma levels, however the study subjects were aware they were receiving different formulations of the same drug.

geometric least squares means for the PKs for tamsulosin ranged from 93 to 111% and were well within the level of bioequivalence of 80 to 125%.

An open label, single dose, 2-way crossover study (**ARI10021**) investigated the pharmacokinetics of oral Flomax (tamsulosin 400 mg capsule – US) and Omnic (tamsulosin 400 mg capsule – Germany) in 27 healthy male subjects, aged 18 to 45 years.

The T_{max} , following oral administration of Flomax (400 mg) under fasting conditions was observed between 3 and 7 hours. Similarly, following oral administration of Omnic (400 mg) under fasting conditions, T_{max} was attained between 3 and 8 hours after dosing. Thereafter, plasma concentrations decreased in an apparently monoexponential manner for both Flomax and Omnic. Values for $t_{1/2}$ ranged from 6.74 to 22.99 hours for Flomax and from 7.39 to 17.76 hours for Omnic. C_{max} and AUCs were also similar for the two formulations.

For the comparison of Flomax versus the Omnic treatment the LS means ratios for C_{max} and AUC were 0.99 and 1.04, respectively, indicating that Flomax and Omnic were bioequivalent, as the 90% confidence intervals for the estimates ranged between 0.93 and 1.08.

Summary of the Pharmacokinetic Studies

Bioequivalence between the combination tablet (Duodart) and co-administration of dutasteride and tamsulosin was established. Food had no effect on the AUC and T_{max} of DTC, however, it reduced C_{max} by approximately 30%.

The percentage of enteric coating (10 or 15%) did not affect the pharmacokinetics of DTC whereas the presence of the emulsifying agent levels of Capmul MCM in the formulation reduced the C_{max} compared with standard soft gelatine capsules.

The source of tamsulosin had no effect on its pharmacokinetics.

Efficacy

Efficacy Overview

Evidence to support the efficacy of co-administration of dutasteride and tamsulosin in the treatment of BPH was submitted in the data from the pre-defined 2-year analyses of one pivotal long-term study, ARI40005, and from two supporting studies, ARI40002 and ARI40013. A number of different scoring systems were used in these trials to assess symptoms of BPH.

The International Prostate Symptom Score (IPSS) was used as a key outcome measure for all three studies.^{22,23} This is a validated 8-item instrument designed to quantify urinary symptoms (essentially the same as the American Urological Association Symptom Index, AUA-SI), but with an independent eighth question related to quality of life (IPSS-QOL). Total score (excluding question 8) ranges from 0 to 35, with higher scores indicating greater impairment.

The BPH Impact Index (BII) was used in studies ARI40005 and ARI40013. This is a validated 4-item instrument to assess the overall impact of BPH on a subject's sense of well

²² Badia X, Garcia-Losa M, Dal-Re R. Ten-language translation and harmonization of the international prostate symptom score: developing a methodology for multinational clinical trials. *Eur Urol* 1997; 31: 129-140.

²³ Barry MJ, Fowler FJ, O'Leary MP et al. The American Urological Association Symptom Index for benign prostatic hyperplasia. *J Urology* 1992; 148: 1549-57.

being, and measures physical discomfort and impact on usual activities.²⁴ Scores range from 0 to 13, with higher scores reflecting greater impact.

The BPH-related Health Status (BHS) was used in study ARI40005 and it has a total score range of 0 to 6 with higher scores reflecting greater impact of BPH on quality of life.

Pivotal Trial - Study ARI40005

This is a Phase III study designed to assess the efficacy of combination treatment with dutasteride 500 µg and tamsulosin 400 mg over dutasteride 500 µg or tamsulosin 400 mg alone. It is an ongoing international, multicentre, randomised, double-blind, parallel group study on improvement of symptoms and clinical outcome in men aged 50 years or older, with moderate to severe symptomatic BPH. The pre-defined year-2 analysis of this ongoing trial was presented for evaluation. The study period to Year 2 was from November 2003 to January 2007, and the study was performed in accordance with GCP guidelines.

Inclusion criteria were males aged ≥ 50 years, diagnosed with moderate-to-severe BPH, with IPSS at screening ≥ 12 , prostate volume (PV) ≥ 30 cc, prostate specific antigen (PSA) ≥ 1.5 ng/mL and ≤ 10 ng/mL, peak urinary flow rate (Q_{\max}) > 5 mL/sec and < 15 mL/sec and minimum voided volume of ≥ 125 mL. Patients had to be able to tolerate oral medication and be willing to participate in the study for 4 years. Exclusion criteria included, a history or evidence of prostate cancer, previous prostatic surgery, PSA > 10 ng/mL and other significant, unstable, serious co-existing medical condition.

The study consists of a 4-week single blind placebo run-in period to reduce any subjective 'placebo response' component in subsequent results reported after randomisation to treatment with active medication. This was then followed by a 4 year double-blind treatment period and a 16-week safety follow up period. The total study duration for each patient will be up to 229 weeks. A placebo control group was not included because the treatment benefits from the therapies being studied have been clearly demonstrated and it was therefore deemed inappropriate to expose this population of men with moderate to severe BPH to undue risk of disease progression and symptoms for a period of 4 years.

Treatment compliance was assessed by a capsule count. Prohibited concomitant medication included other alpha blockers, medications that may interact with alpha-blockers (for example, cimetidine, warfarin) and drugs with antiandrogenic properties. A total of 5064 men were enrolled, of which all except 12 entered the placebo run-in phase; the 12 subjects were randomised to active treatment without entering the placebo run-in phase. Of subjects who entered the placebo run-in, 220 withdrew prior to randomisation. Reasons for withdrawing were other (67 patients), protocol variation (62), withdrawal of consent (49), adverse events (26), lost to follow up (15), and missing (1). The remaining 4844 patients were assigned to study treatment in accordance with a computer generated randomization schedule. The majority of the patients completed the Year 2 visit, and the number of subjects that withdrew prior to this was similar across the treatment groups. The primary reasons for premature discontinuation were adverse events (AEs) and withdrawal of consent. More patients withdrew due to AEs in the combination group (154/1610, 10%) compared with the tamsulosin group (136/1611, 8%) and dutasteride group (108/1623, 7%). The number of patients with major protocol violations resulting in extension for the per protocol set was low and similar across all three treatment groups. The predominant major violation in all groups were deviations from inclusion criteria of $Q_{\max} > 5$ mL/sec and ≤ 15 mL/sec and minimum voided volume of ≥ 125 mL at screening. The majority of subjects in each treatment group

²⁴ Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe L, Mebust WK. Measuring disease-specific health status in men with benign prostatic hyperplasia. *Med Care* 1995; 33: AS145-AS155.

were compliant having taken $>75\%$ and $\leq 125\%$ of allotted study medication. Mean overall compliance was $>96\%$ in all groups.

Baseline demographics were similar across all treatment groups. The majority of the patients were White and 42% were under 65 years of age. Subjects had a diagnosis of BPH for a mean of 3.9 years and the majority of patients were sexually active. Baseline BPH history was similar across the treatment groups. More than half (59%) of the population had concurrent medical conditions, most common being cardiovascular disorders, mainly hypertension, which affected 41% of all patients. At baseline, mean symptom scores, Q_{\max} , and PV were similar across the treatment groups and were indicative of a group with moderate to severe symptoms of BPH.

Efficacy Endpoints & Statistical Considerations

The primary efficacy endpoint of interest at Year 2 was improvement in symptoms as determined by change from baseline in International Prostate Symptom Score (IPSS). Previous studies have suggested that 3 units is the minimum within-treatment IPSS change in symptom improvement before a difference is perceived, hence the selection of 2 and 3 unit differences in the secondary outcome measure.²⁴ For IPSS, the anticipated superiority of combination therapy over dutasteride monotherapy was 1.5 units and for tamsulosin monotherapy was 1.0 unit.

Key secondary outcome measures were change from baseline in PV and Q_{\max} ; proportion of patients with IPSS improvement from baseline ≥ 2 units, ≥ 3 units, and $\geq 25\%$; and the proportion of subjects with Q_{\max} improvements from baseline of $\geq 30\%$ and $\geq 3\text{mL/sec}$; and health outcome measures such as BPH Impact Index (BII), BPH-related Health Status (IPSS-QOL) and the Patient Perception of Study Medication (PPSM), which is a tool that was developed by the sponsor specifically for this study to quantify patient perception and satisfaction with the effect of the study treatment.

It was calculated that approximately 4500 enrolled subjects, 1500 per treatment group, would provide 91% power to declare superiority of the combination therapy versus both monotherapies at Year 2. The intention to treat (ITT) population consisted of all patients randomised to the double-blind treatment phase, and was the primary analysis population for efficacy and safety.

The ITT population was the primary population for analysis of efficacy and safety. Statistical testing of the multiple primary, secondary and of multiple time points for each endpoint were performed in a pre-determined hierarchical step down manner at the 0.01 level of significance. Analysis of data was performed using two different approaches for missing data: last observation carried forward (LOCF) and At Visit where missing values were not replaced. Change in baseline IPSS, Q_{\max} , BII and BHS were compared at each scheduled assessment point for combination therapy versus monotherapy using t-tests from a general linear model with effects for adjustment, cluster and baseline value at $\alpha = 0.01$. The adjusted mean estimates, adjusted mean differences, and 95% confidence intervals were presented. The adjusted mean differences were in terms of combination therapy minus monotherapy.

Primary Efficacy Outcomes

The primary outcome measure of interest at Year 2 was combination therapy versus each monotherapy for change from baseline of IPSS. Although IPSS improvement categories were secondary endpoints, they were presented in the primary efficacy section to provide a more comprehensive overview of improvement in symptom as measured by IPSS.

At Month 24, statistically significant ($p < 0.01$) greater reduction from baseline in IPSS was observed with combination therapy compared with either dutasteride or tamsulosin monotherapy.

For LOCF analysis, the mean change from baseline for IPSS was -6.2, -4.9 and -4.3 with combination therapy, dutasteride monotherapy and tamsulosin monotherapy, respectively. This represents an adjusted mean difference between combination and dutasteride of -1.3 points (95% CI -1.69, -0.86. $p < 0.001$). The adjusted mean difference between combination therapy and tamsulosin was -1.8 points (95% CI -2.23, -1.40. $p < 0.001$). This is summarised in Table 4, along with values for at visit analysis. Regarding the superiority of combination therapy versus dutasteride alone, the adjusted mean difference of -1.3 does not meet the pre-defined superiority margin of 1.5 points for LOCF analysis, although the data for At Visit analysis does reach this difference. In both LOCF and At Visit analysis, the pre-defined superiority measure of 1.0 point for combination therapy over tamsulosin monotherapy was reached in both analyses.

Table 4: IPSS change from baseline at month 24 (ITT population) – ARI40005

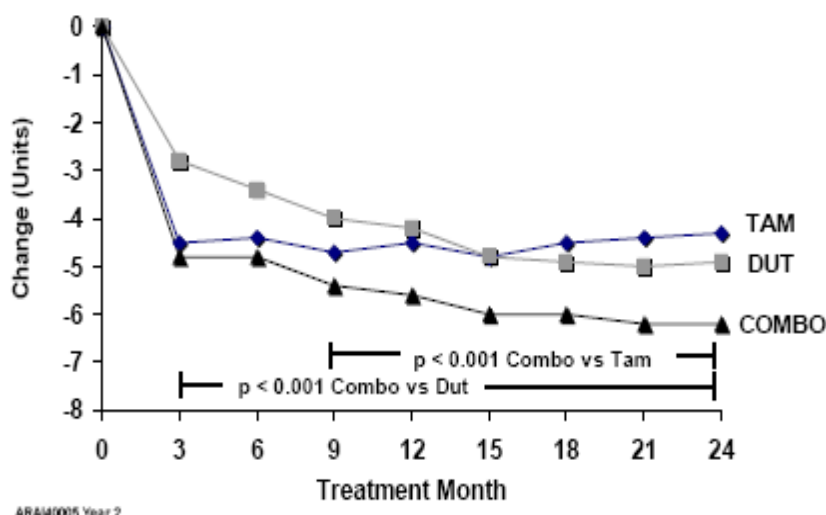
Change from Baseline Analysis	Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611
LOCF, n	1575	1592	1582
Adjusted mean (units)	-6.2	-4.9	-4.3
Adj mean difference ^a	---	-1.3	-1.8
[95% CI]	---	[-1.69, -0.86]	[-2.23, -1.40]
p-value vs. combo ^b	---	<0.001	<0.001
At Visit, n	1258	1287	1237
Adjusted mean (units)	-6.8	-5.3	-5.0
Adj mean difference ^a	---	-1.5	-1.9
[95% CI]	---	[-1.93, -1.08]	[-2.28, -1.43]
p-value vs. combo ^b	---	<0.001	<0.001

a. Combination minus each monotherapy

b. Based on t-test from general linear model (Change from baseline IPSS = treatment + cluster + baseline IPSS)

IPSS scores at each post-baseline assessment from Month 3 to Month 24 were consistently lower in the combination group compared to each monotherapy group. The reductions in IPSS were statistically significant for combination versus dutasteride from Month 3 onwards, and improved continually until Month 24. The reductions in IPSS for combination therapy versus tamsulosin were statistically significant from Month 9. This is demonstrated in Figure 1.

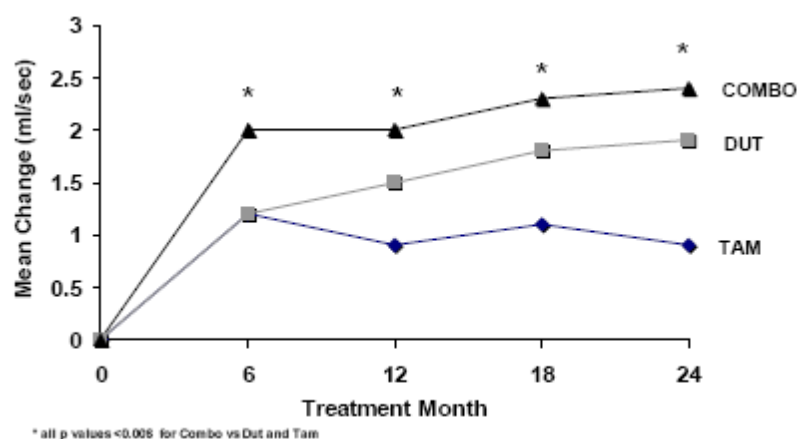
Figure 1: Mean change from baseline in IPSS (LOCF) – ARI40005



At Month 24, a statistically significantly greater proportion of subjects treated with combination therapy had IPSS improvement of ≥ 2 units, ≥ 3 units, and $\geq 25\%$ from baseline compared to either monotherapy. Compared to dutasteride monotherapy, the proportion of patients with IPSS improvements of ≥ 2 units, ≥ 3 units, or an improvement of $\geq 25\%$ from baseline was statistically significantly higher on combination therapy at Month 3, and was sustained to Month 24. Compared to tamsulosin monotherapy, the proportion of patients with IPSS improvements of ≥ 2 units, ≥ 3 units, or an improvement of $\geq 25\%$ from baseline was statistically significantly higher on combination therapy at Month 9, and was sustained to Month 24.

Secondary Efficacy Outcomes

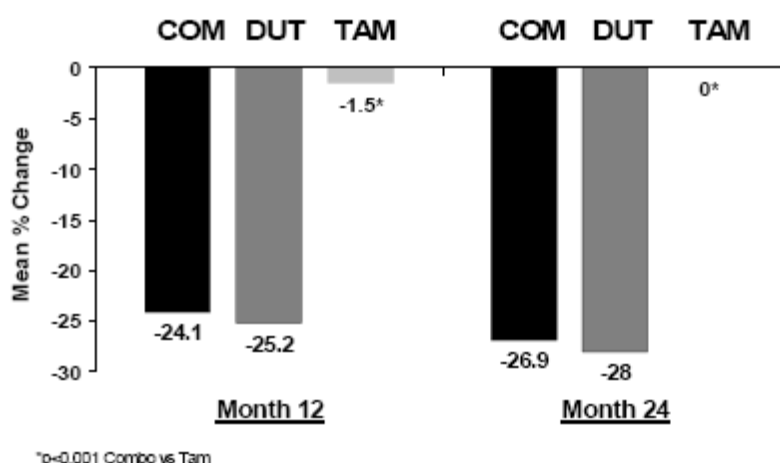
Changes (increases) in peak urinary flow rate (Q_{\max}) from baseline were consistently higher on combination therapy compared to either monotherapy at each 6 month assessment, and this was continued over the 24 month period (Figure 2). At Month 24, the adjusted mean change from baseline in Q_{\max} was 2.4 mL/sec for combination therapy, compared to 1.9 mL/sec for dutasteride monotherapy, and 0.9 mL/sec for tamsulosin. These increases in Q_{\max} were statistically significant between combination therapy and both monotherapies at each assessment point from Month 6 to Month 24.

Figure 2: Change from Baseline in Q_{\max} (LOCF) – ARI40005

The proportion of patients with improvements in Q_{\max} of 30% or ≥ 3 mL/sec compared to baseline was statistically significantly higher on combination therapy than on tamsulosin alone at each 6 month assessment point up until 24 months. A statistically significant difference at 24 months between combination therapy and dutasteride alone with regard to these endpoints could not be demonstrated due to *a priori* defined multiplicity guidelines.

With regard to prostate volume (PV) the observed mean PV at Months 12 and 24 showed similar reduction from baseline for both the combination group and the dutasteride monotherapy group. However, tamsulosin monotherapy showed no reduction in PV from baseline to Month 24 and both combination therapy and dutasteride monotherapy showed statistically significantly greater reduction in PV compared with tamsulosin monotherapy. These results are depicted in Figure 3.

Figure 3: Adjusted mean percentage change from baseline in prostate volume (LOCF, ITT population) – ARI 40005



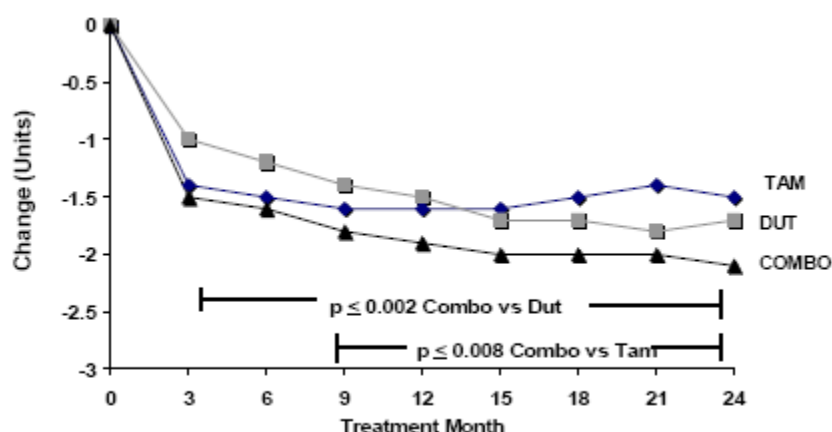
Health Outcomes

The health outcome measures at the Year 2 analysis were change from baseline in BII, BHS (QOL Q8 of IPSS) and Patient Perception of Study Medication (PPSM).

Baseline BII values were similar across all treatment groups. BII scores at each 3 month assessment period were consistently lower in the combination group compared to either

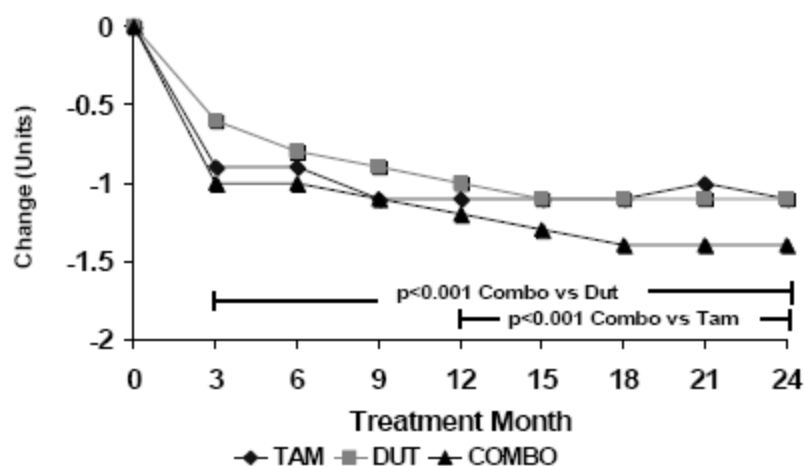
monotherapy (Figure 4). The adjusted mean changes (reductions) in BII were statistically significantly greater on combination therapy compared to either monotherapy after 24 months, the adjusted mean improvement from baseline was -2.1 points, -1.7 and -1.5 in the combination group, dutasteride monotherapy and tamsulosin monotherapy groups, respectively. Statistically significant differences between combination therapy and dutasteride monotherapy were observed at all 3 month intervals from month 3 onwards. Statistically significant differences between combination therapy and tamsulosin monotherapy were reached from month 9 onwards.

Figure 4: Adjusted mean change from baseline in BII (LOCF) – ARI40005



Baseline BHS values were similar across all treatment groups. Reductions from baseline in BHS were consistently numerically lower with combination therapy compared to either monotherapy and continued over the 24 month period (Figure 5). At Month 24, the reduction in BHS from baseline with combination therapy was statistically significantly greater than with either monotherapy, with adjusted mean change being -1.4 points with combination therapy compared to -1.1 points in both monotherapy groups. Statistically significant differences were observed between combination therapy and dutasteride from Month 3 onwards. Statistically significant differences were observed between combination therapy and tamsulosin from Month 12 onwards.

Figure 5: Adjusted mean change from baseline in BHS (LOCF) – ARI40005



PPSM expectations at screening were similar across all treatment groups. The proportion of patients who expressed any satisfaction, or felt that they had shown an improvement in their symptoms at month 24 was statistically significantly higher in the combination group compared with either monotherapy, except for change in pain prior to urinating. However, there is no reference made in the submission to any external validation of this scoring system, so the evaluator advised caution in the interpretation of any results or conclusions drawn from this information.

Non-Pivotal Trials - Study ARI40002

This study was a short-term pilot, multicentre, double-blind, parallel group, randomised study to investigate the effect on urinary symptoms of discontinuing tamsulosin, following 24 weeks of combination treatment with 500 µg dutasteride and 400 mg tamsulosin daily in subjects with BPH. The two treatment groups were to receive either 36 weeks of combination therapy with dutasteride 500 µg daily and tamsulosin 400 mg daily (TD36 group), or 24 weeks of combination therapy followed by 12 weeks of dutasteride 500 µg daily monotherapy (TD24+D12 group). The study was conducted in accordance with GCP guidelines and all applicable declarations, and the study period was between February 2000 and September 2001.

Inclusion criteria were male ≥ 45 years of age, with a diagnosis of BPH according to history and clinical examination (including digital rectal examination, DRE), with IPSS ≥ 12 , enlarged PV ($>30 \text{ cm}^3$) as determined by DRE. Exclusion criteria included any history or evidence of prostate cancer, PSA $<1.5 \text{ ng/mL}$ or $>10.0 \text{ ng/mL}$, a history of urethral instrumentation within 7 days of screening or episode of AUR within 3 months of screening, use of medications which may interact with either study medication, or any significant medical comorbidities.

The study commenced with a 4 week single-blind placebo run in period prior to randomisation to one of the study groups. The last 12 weeks of the study where the two treatment groups were taking different medications was performed in a double-blind manner. Once randomised, patients were to self administer active study medication for 36 weeks and then a further week of placebo. Patients were assessed as outpatients at screening, baseline, and then at 4, 12, 24, 30, 36 and 37 weeks post baseline. Use of other BPH treatments was forbidden during the study, as was use of medications thought to have an interaction with tamsulosin. Treatment compliance was assessed using capsule counts.

A total of 421 patients were enrolled and entered the placebo run-in phase of the study, of which 94 discontinued prior to randomisation. The main reason for discontinuing was a PSA <1.5 or $>10.0 \text{ ng/mL}$ (66/421 patients). Other reasons, each reported by $\leq 2\%$ of the patients were AEs, withdrawal of consent, lost to follow up and major protocol variation. The remaining 327 patients were randomised and comprise the ITT population for analysis. Major protocol violations were reported for 23/327 (7%) subjects overall [11/164 in TD36 group (7%); 12/163 in TD24 and D12 group (7%)], which resulted in their exclusion from the PP population. Main violations reported were concurrent use of drugs with anti-androgenic properties or anabolic steroids (5 patients in each group) and use of alpha-agonists within 48 hours prior to any visit (5 patients in each group). The treatment blinding was not broken for any patients. The compliance with study medication was calculated at each visit by counting the number of capsules returned. Mean study drug compliance for dutasteride and tamsulosin or matched placebos from baseline to end of active treatment was 98%. Baseline demographic data for the two groups were. Current medical conditions were reported by the majority of patients at screening (82%), with similar numbers in each treatment group (80% in TD 36 group, 83% in TD 24+D12 group).

Efficacy endpoints and statistical considerations

The primary objective was to assess any difference at 30 weeks post baseline, in the proportion of patients experiencing an improvement or no change in their urinary symptoms (as perceived by the patients themselves), following discontinuation or continuation of tamsulosin for the two groups. This was assessed according to response to the question: *“Over the past 2 weeks, on average have you felt better, worse, or the same, with respect to your urinary symptoms, than at your last visit?”* It should be noted that this question had not been externally validated as an indication of treatment success or satisfaction. These data were analysed using a Mantel-Haenszel test controlling for country. The hypothesis being tested was that there is no association between a patient’s response to the primary efficacy question and their randomised treatment group. The lower 97.5% confidence limit was used to conclude if dutasteride-only treatment was non-inferior or clinically as good as combination therapy. If the lower 97.5% confidence limit was less negative than -0.20, then non-inferiority could be claimed.

Secondary endpoints included:

- (i) mean change in IPSS for patients within each treatment group from 24 weeks post baseline to 30 and 36 weeks post baseline,
- (ii) mean change in IPSS for all patients between baseline and 4, 12, and 24 weeks post baseline, (iii) proportion of all subjects in each treatment group experiencing an improvement or no change in their symptoms at 36 weeks post baseline,
- (iv) proportion of patients in each treatment group who expressed a preference for the regimen received within the first 24 weeks when questioned at week 30 as shown in response to the question: *“did you prefer the medication you were taking up to your last visit more than the medication you are now taking?”*
- (v) mean change in IPSS-QOL score in each treatment group between 24 and 36 weeks post baseline, and
- (vi) mean change in QOL question score for all patients between baseline, and 4, 12 and 24 weeks post baseline.

Although the study was a pilot study, it was calculated that 200 subjects were required to enable the study to show that following combination therapy for 24 weeks, single treatment with dutasteride was clinically as good as combination relative to the primary endpoint. This was based on CI of 95% and power of 80%. To allow for drop out of 25%, a target sample size of 250 patients was chosen. The intention to treat (ITT) population was considered the primary efficacy and safety population, and consisted of all patients randomised to treatment after the 4 week placebo run-in period. For a non-inferiority study, the per protocol (PP) study population usually provides a better indication.

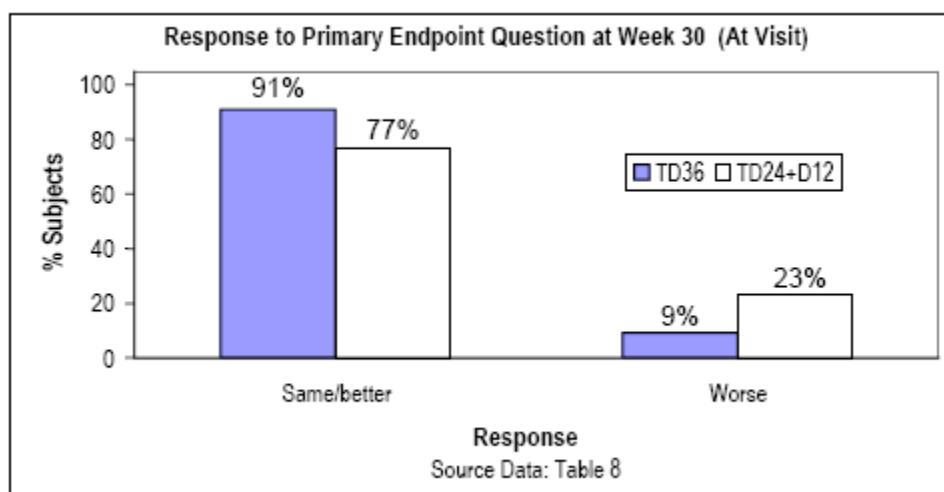
Primary Efficacy Outcomes

After 24 weeks of combination therapy, a similar number in each treatment group felt the same or better at Week 24 compared to the previous visit (TD 36: 89%, TD24+D12: 87%) which suggests that the patients were well balanced with regard to response to combination therapy across both groups.

At Week 30, 91% (139/154) patients who continued combination therapy after 24 weeks (TD 36 group), felt the same or better regarding urinary symptoms than at the previous visit. In the group who discontinued tamsulosin after Week 24 (TD24+D12 group), 71% (115/151) felt the same or better than at the previous visit. This is displayed in Figure 6. These data were analysed using a Mantel-Haenszel test controlling for country, and the difference in

proportion was -0.11 ($p=0.001$; 95%CI: -0.18, -0.04), demonstrating non-inferiority of dutasteride-only treatment compared to the combination therapy.

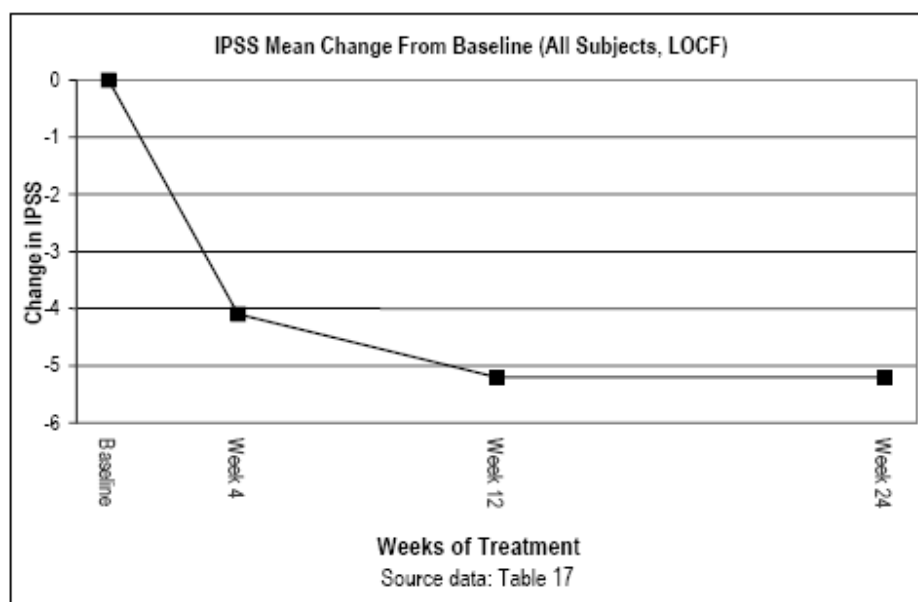
Figure 6: Response to primary end-point question at week 30 – ARI40002



Secondary Efficacy Outcomes

With regards to change in IPSS from baseline with time, continuous, consistent improvements in IPSS were observed from baseline to Week 24 in both groups (Figure 7). At baseline, the mean IPSS score was 16.4 in the TD36 group and 16.5 in the TD24+D12 group, and at Week 24, the mean IPSS value was 11.2 in both groups. After Week 24, when treatment changed in the TD24+D12 group to receiving dutasteride monotherapy, the IPSS mean scores were slightly higher in this group compared to the group that continued combination therapy.

Figure 7: Mean change in IPSS from Baseline – ITT population, LOCF – ARI40002



At Week 30, in the TD24+D12 group who had ceased tamsulosin 6 weeks earlier, there was an adjusted mean change in IPSS from Week 24 of +1.2 points (that is, worsening of symptoms), compared to the TD36 group who showed continued improvement with an adjusted mean change in IPSS from Week 24 of -0.5 points. The adjusted mean difference

between the groups was 1.6 points which was statistically significant ($p < 0.001$; 95% CI: 0.8, 2.5). At Week 36, there was an improvement in IPSS in both groups from Week 30. The overall adjusted mean change in IPSS from Week 24 was -0.9 in the TD 36 group and 0.0 in the TD24+D12 group.

Mean change in the IPSS-QoL question from baseline was carried out at Weeks 4, 12, 24, 30 and 36 using LOCF approach. The score for this question consistently improved from baseline in all subjects during the 24 week combination phase of the treatment. At Week 30, the adjusted mean change from Week 24 in the TD36 group was -0.1 compared to 0.1 in the TD24+D12 group. At Week 36, the adjusted mean change from Week 24 was -0.1 in both groups.

Regarding treatment preference, patients were asked at Week 24 and Week 30 if they had any preference for the treatment received up to the last visit compared to that taken in the most recent period. At Week 24, 79% of subjects in both treatment groups did not prefer the medication they had taken up to Week 12 to their current treatment, demonstrating that both treatment groups were well balanced before changing treatments. At Week 30, 71% of patients in the dutasteride-only group did not prefer the medication they had taken up to Week 24 (combination). Similarly, 81% of patients receiving combination treatment after Week 24 did not prefer the medication they had taken up to Week 24.

Non-Pivotal Trials - Study ARI40013

This study was an open label multicentre Phase IIIb study to evaluate the safety and efficacy of dutasteride with or without tamsulosin in the treatment of a large cohort of patients with symptomatic BPH under routine clinical conditions. Patients were assigned to a treatment regimen for at least 36 weeks based on their baseline IPSS-QOL score. If the IPSS-QOL was < 4 points they were to receive monotherapy with dutasteride 500 μg once daily (od) [monotherapy group, MT]. If the IPSS-QOL was ≥ 4 points they were to receive combination therapy with dutasteride 500 μg od plus tamsulosin 400 mg od for 24 weeks, followed by dutasteride monotherapy for the remaining 12 weeks [combination therapy group, CT]. The study was conducted in accordance with all GCP guidelines and the study was conducted between March 2002 and March 2003.

Inclusion criteria were age > 50 years, diagnosis of BPH based on history and physical examination (including DRE), IPSS of > 7 at screening, a PSA between 1.5 ng/mL and 10.0 ng/mL , PVR of < 200 mL . Exclusion criteria included history or evidence of prostate carcinoma, urethral instrumentation within 14 days of screening, previous treatment with 5-ARI, and other significant comorbidity. Prohibited concomitant medication included other alpha blockers, medications that may interact with alpha-blockers (for example, cimetidine, warfarin) and drugs with antiandrogenic properties.

A total of 2403 subjects were initially screened, and of these, 2385 patients were considered eligible for participation in the study. Of these 2385 patients, 811 were assigned to receive dutasteride monotherapy (MT), and 1574 were assigned to the dutasteride/ tamsulosin combination therapy group (CT). These numbers met the expected ratio of 1:2 (MT:CT) according to baseline severity. A total of 713 patients in the MT group and 1291 patients in the CT group completed the study. Demographics of patients included were similar between the treatment. As expected by the treatment assignment criterion, patients assigned to receive combination therapy had higher baseline values for efficacy variables such as IPSS-QOL, IPSS, and BII compared with patients assigned to receive monotherapy.

Efficacy endpoints and statistical considerations

The primary efficacy outcomes were changes from baseline in the IPSS and BII after 36 weeks of treatment. Secondary outcome measures included changes from baseline in IPSS and BII over the entire study period, number of patients requiring surgery or experiencing AUR during the treatment; changes in prostate volume (PV) and post-void residual volume (PVR) were analysed.

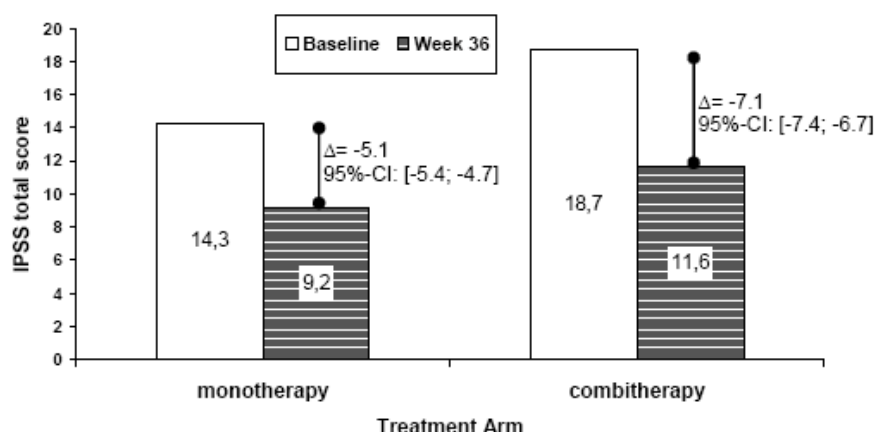
The planned sample size was 3000, although no statistical sample size calculation was performed as there was no statistical hypothesis generated. The sample size of 3000 was chosen as it was considered to potentially identify hypothetical rare adverse events (occurring with an incidence of 0.1%) with a probability of 90%. The ITT population was to consist of all patients assigned to one of the treatment groups who received at least one dose of the study medication. For this population, the LOCF method was used to account for any missing values for IPSS and BII for the primary efficacy endpoint. Other analysis populations were defined, but for the purposes of this evaluation, the ITT population will be the focus.

The primary statistical analysis referred to pre-post comparisons of IPSS and BII within the two treatment groups by calculating confidence intervals of the respective estimates. Inferential statistical analyses for treatment comparisons were not performed. The pre-planned individual treatment duration was 36 weeks, but an extension of the treatment for a further 12-36 weeks was allowed in case of a pending market authorisation of dutasteride at the time of Visit 5 (Week 36). This made the maximum individual treatment duration 72 weeks.

Primary Efficacy Outcomes

At Week 36, both the treatment groups showed statistically significant reductions in the primary efficacy variables, with negative 95% CI values that did not cross zero. In the monotherapy group, the mean total IPSS had changed by -5.1 [95%CI:-5.4, -4.7] and the mean BII had changed by -2.3 [95%CI: -2.5, -2.1]. In the combination group the mean total IPSS had changed by -7.1 [95%CI:-7.4, -6.7] and the mean BII had changed by -2.3 [95%CI: -3.6, -3.3]. These changes are displayed graphically in Figure 8.

Figure 8: Mean changes in IPSS total scores by treatment groups from baseline to week 36 (ITT, LOCF) – ARI40013

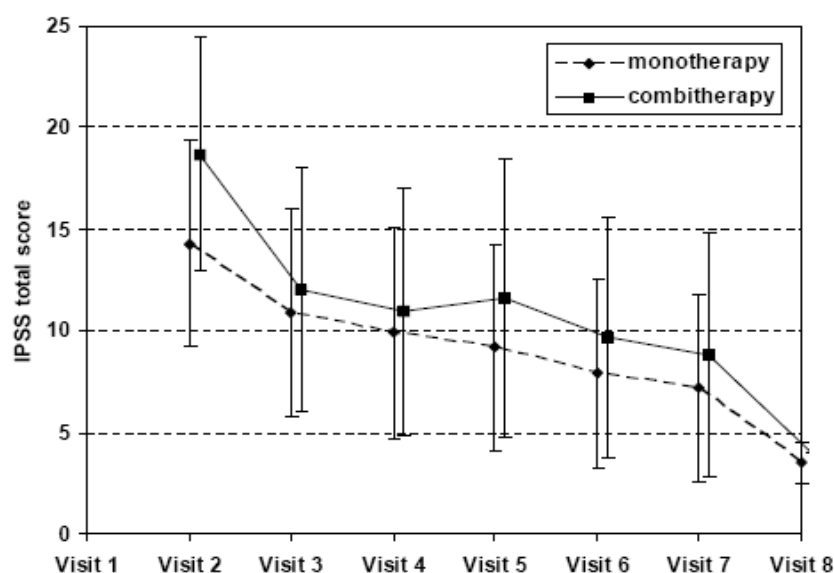


Descriptively, the mean reduction was stronger in the CT group compared to the MT group, but it was stated in the submission, and agreed by the evaluator, that this is most likely explained by the patients in the CT group starting with higher baseline values, indicating worse symptoms. Therefore the evaluator recommended that no conclusions on differences in efficacy between the two treatments should be drawn from this data.

Secondary Efficacy Outcomes

Changes in IPSS and BII over time were initially defined as secondary outcome measures, although in the submission they were analysed with the primary outcome measure. The change in total IPSS and BII values with time are displayed graphically in Figures 9 and 10. It can be noted that in the CT group, there was a slight increase in the BII and IPSS from Week 24 to Week 36, which corresponds to the withdrawal of tamsulosin from their treatment regimen.

Figure 9: Course of IPSS total score with LOCF up to Visit 5 (Week 36) – ARI40013



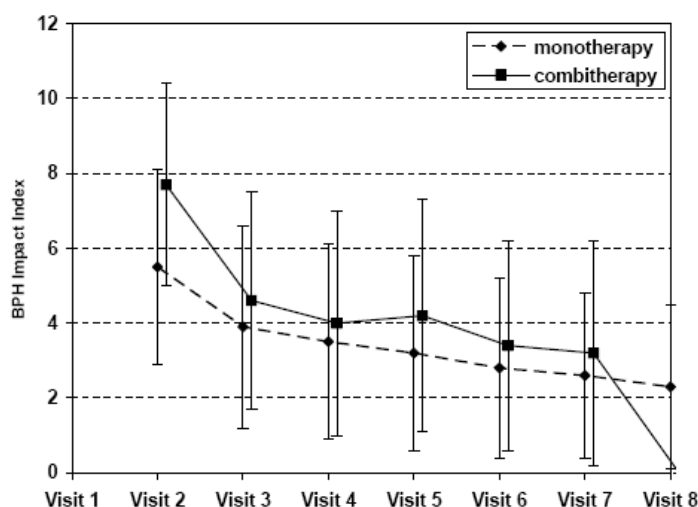
Note: Data given as arithmetic mean and standard deviation.

Note: The number of observations decreased considerably from Visit 5 onwards:

Monotherapy: Visits 2-5: N=808; Visit 6: N=351; Visit 7: N=45; Visit 8: N=4

Combitherapy: Visit 2: N=1,564; Visits 3-5: N=1,565; Visit 6: N=614; Visit 7: N=80; Visit 8: N=2

Figure 10: Course of BII with LOCF up to Visit 5 (Week 36) – ARI40013



Note: Data given as arithmetic mean and standard deviation.

Note: The number of observations decreased considerably from Visit 5 onwards:

Monotherapy: Visit 2: N=793; Visit 3: N=803; Visits 4-5: N=805; Visit 6: N=346;

Visit 7: N=43, Visit 8: N=4

Combitherapy: Visit 2: N=1,516; Visit 3: N=1,549; Visit 4: N=1,551; Visit 5: N=1,553;

Visit 6: N=608; Visit 7: N=76; Visit 8: N=2

The evaluator recommended caution in interpreting any data from these figures beyond Visit 5 (Week 36) because this is a voluntary extension, and as mentioned in the notes accompanying the figures, the numbers analysed reduce dramatically. There is no discussion in the submission as to reasons why certain patients decided to extend treatment. In fact at Visit 8, the final plot on these figures, the numbers involved are 2 patients in the CT group and 4 in the MT group. The evaluator recommended disregarding any data presented after Visit 5 (Week 36).

There was also a reduction in the other pre-defined secondary efficacy variables of IPSS-QoL, PV and PVR in both treatment groups. These reductions were comparable in the two groups. The mean PV changed from baseline to study end by 15.1 mL (± 13.9) (mean percentage change -25.4%) in the MT group and by -15.8 mL (± 16.6) (mean percentage change -25.5%) in the CT group. The PVR changed by -21.3 ± 47.9 mL in the MT group and by -21.7 mL (± 54.8) in the CT group. The 95% confidence intervals for the changes in mean in both PV and PVR indicated statistically significant changes from baseline in both treatment groups. No comparison is offered between the treatment groups, which seems appropriate to the evaluator as the two treatment groups were not matched for disease severity at baseline.

The overall rate of patients experiencing AUR during the study was 0.5% in the MT group (4 patients) and 1.7% in the CT group (26 patients). It is difficult to draw any meaningful conclusions from these data due to the fact that treatment groups were defined by severity of symptoms, and the increased number of patients experiencing AUR in the CT group again likely reflects that this was the group that had more significant disease at baseline. Prostate surgery was documented for one subject in each treatment group.

Efficacy Conclusions

After 2 years of treatment in the pivotal study ARI40005, combination therapy with dutasteride and tamsulosin was statistically significantly superior to either monotherapy with

regard to symptom improvement (as evidenced by reduction in IPSS) and improvement in urinary flow rate (Q_{\max}) and proportion of subjects with clinically relevant ≥ 2 units, 3 units and 75% improvement in IPSS as well as $>30\%$ and $>3\text{mL}$ improvement in Q_{\max} .

However, it should be noted that in study ARI40005, the adjusted mean difference in IPSS between combination therapy and dutasteride monotherapy of -1.3 did not reach the pre-defined anticipated superiority of -1.5 when using LOCF analysis.

Combination therapy with dutasteride and tamsulosin was significantly superior to tamsulosin monotherapy at reducing prostate volume, and was comparable to dutasteride monotherapy (Study ARI40005).

Data regarding health outcome measures for study ARI40005 also demonstrated that combination therapy with dutasteride and tamsulosin was statistically significantly superior to either monotherapy on improvement in health outcomes as measured by previously validated scores using BII and BHS scores.

Data from the short-term pilot study ARI40002 provided supportive evidence of efficacy of combination therapy with dutasteride and tamsulosin in treating symptoms of BPH over a short period of 24-36 weeks.

In study ARI40002, 77% of patients felt the same or better in the 6 weeks following ceasing tamsulosin than they did at Week 24, compared to 91% of patients who continued on combination therapy. Despite a p-value of 0.001, the CIs did not exceed the pre-defined equivalence criteria set to demonstrate non-inferiority.

Study ARI40002 also demonstrated that once tamsulosin was stopped after 24 weeks, patients had an increase in their symptom score that was statistically significantly higher than patients who continued combination therapy.

Data from study ARI40013 demonstrates efficacy of combination therapy in treating patients over a short period of 36 weeks with a combination of dutasteride and tamsulosin. However, in view of the difference in baseline disease severity between the two treatment groups, the open-label design, and absence of any statistical comparison, no conclusions from this study can be drawn regarding any increase in benefit of combination therapy compared to monotherapy.

Safety

The AE profiles for both dutasteride and tamsulosin are well documented. The most reported AEs for dutasteride are primarily related to sexual function (impotence, altered libido, ejaculation disorders) and gynaecomastia. These events, together with incidence of prostate cancer, are defined as AEs of special interest in clinical trials involving dutasteride. The most common AEs described for tamsulosin are headache, dizziness, rhinitis, infection, abnormal ejaculation and asthenia. Other important AEs which are reported less frequently include orthostatic hypotension and syncope.

The target population for these drugs are ageing men with BPH, and comorbidities are prevalent in this population, which may complicate the interpretation of safety data. Common conditions include hypertension, ischaemic heart disease, diabetes, COPD, cancer and cerebrovascular disease.

Data in this submission to support the safety of co-administration of dutasteride and tamsulosin are provided in the pre-defined 2-year analysis of data from the pivotal study ARI40005, and the supporting studies ARI40002 and ARI40013. There was no integration of data across these studies because of differences in design and treatment schedules.

All three studies included treatment-emergent adverse events, laboratory data and vital signs. A drug-related AE was an event considered by an investigator to have a reasonable possibility of being related to the study medications.

Additionally, study ARI40005 included measures of total serum PSA and post-void residual volume. Cardiovascular events were analysed as events of special interest in study ARI40005 to address any possibility of long-term reduction of DHT leading to a relative hypogonadal state and increased risk of cardiovascular events.

Pivotal Study - Study ARI40005

Drug Exposure

In total 4844 patients were randomised to receive one of the study treatment regimens, with 1610 being randomised to receive combination therapy with dutasteride and tamsulosin, 1623 receiving dutasteride alone and 1611 receiving tamsulosin alone. Overall mean exposure to investigational product was similar across the treatment groups with >80% of patients in each treatment group being treated for >720 days.

Overview of Adverse Events

At the pre-defined 2 year analysis point, the overall incidence of AEs and SAEs, including deaths, was similar across the three treatment groups at 63-65% (Table 5). The incidence of drug-related AEs was statistically significantly higher in the combination group (24%) compared to each monotherapy group (18% in the dutasteride group and 16% in the tamsulosin group). The overall incidence of AEs and drug related AEs was higher in all groups in Year 1 compared with Year 2, and this is illustrated in Figure 11.

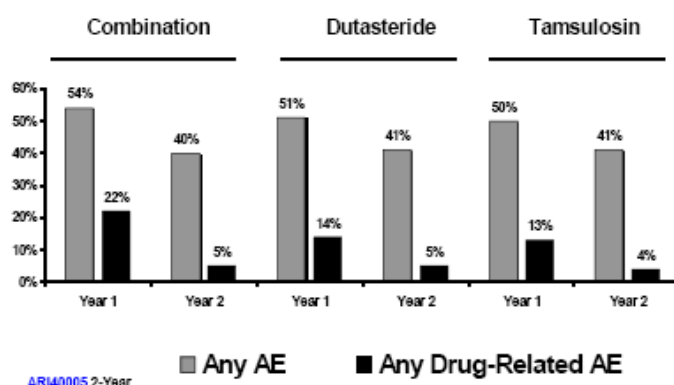
Table 5: Number (%) of patients with AEs by type (ITT population) – ARI 40005

AE type	Combination N=1610	Dutasteride N=1623		Tamsulosin N=1611	
	n (%)	n (%)	p-value	n (%)	p-value
Any AE	1048 (65)	1039 (64)	0.53	1011 (63)	0.17
Any drug-related AE	391 (24)	291 (18)	<0.001	259 (16)	<0.001
Any SAE	188 (12)	196 (12)	0.74	207 (13)	0.33
Deaths	20 (1)	19 (1)	-	21 (1)	-
Any AE withdrawal from study	164 (10)	127 (8)	0.020	148 (9)	0.34
Any AE withdrawal from study drug	159 (10)	123 (8)	0.021	143 (9)	0.33

Treatment-emergent defined as AEs with onset on or after randomisation (or missing onset of treatment date).

1. Combination versus each monotherapy were compared using Fisher's exact test.

Figure 11: Overall incidence of AEs and Drug related AEs in Year 1 and Year 2 (ITT population) – ARI40005



Source: Study ARI40005 Table S5

The most frequently reported adverse effects by Preferred Term (PT) across the three treatment groups were erectile dysfunction (4-8%), hypertension (5-6%) and nasopharyngitis (5-6%). The most common AEs are summarised in Table 6. The incidence of erectile dysfunction was significantly higher in the combination group (8%) than in the tamsulosin group (4%) ($p < 0.001$). The incidence of retrograde ejaculation, ejaculation failure and decreased semen volume was also higher on combination therapy than with either monotherapy. The incidence of other AEs was similar across the treatment groups. The incidence of adverse events by system organ class was similar across all three treatment groups, although more patients in the combination group had reproductive and breast disorders compared to each monotherapy group.

Table 6: Number (%) of patients with Common AEs (>3% in any group) by preferred term (ITT population). ARI 40005

Preferred Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any AE	1048 (65)	1039 (64)	1011 (63)
Erectile dysfunction	132 (8)	118 (7)	72 (4)
Hypertension	81 (5)	92 (6)	90 (6)
Nasopharyngitis	80 (5)	91 (6)	102 (6)
Retrograde ejaculation	70 (4)	10 (<1)	18 (1)
Back pain	68 (4)	61 (4)	73 (5)
Libido decreased	60 (4)	52 (3)	28 (2)
Influenza	50 (3)	50 (3)	63 (4)
Dizziness	50 (3)	39 (2)	51 (3)
Upper respiratory tract infection	45 (3)	35 (2)	35 (2)
Arthralgia	45 (3)	36 (2)	47 (3)
Ejaculation failure	41 (3)	10 (<1)	14 (<1)
Headache	25 (2)	49 (3)	38 (2)

AEs with onset on or after randomisation (or missing onset of treatment date).

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

At the 2-year data cut-off point, there had been a total of 61 deaths, the majority of which were due to cardiac disorders (24 patients) or neoplasms (14 patients). One death occurred prior to randomisation and was not included in subsequent analysis. The most frequent fatal

AE across all treatment groups was myocardial infarction. There was only one death, from a myocardial infarction in the dutasteride monotherapy group, which was considered by the investigator to have a reasonable possibility of being related to the treatment medication.

The overall incidence of serious adverse effects (SAEs) was similar across the treatment groups, with the most frequently reported SAEs being prostate cancer and myocardial infarction. The incidence of myocardial infarction was similar across the three groups. Regarding prostate cancer, the incidence was lower in the dutasteride monotherapy group compared with the other two groups which were comparable. The incidence of SAEs was higher in patients ≥ 65 years compared to younger patients, and more patients in this older group reported prostate cancer. The incidence of SAEs considered related to the study medication was similar across the treatment groups, and most of these drug related SAEs were disorders of cardiac, nervous or vascular system.

The overall incidence of AEs leading to premature withdrawal from the study was 10% in the combination group, compared to 8% in the dutasteride group and 9% in the tamsulosin group. The most frequently reported AEs leading to withdrawal were erectile dysfunction, prostate cancer and reduced libido. More patients on combination therapy withdrew due to AEs related to sexual function compared to each monotherapy group. More patients withdrew due to AEs during the first year of treatment compared to the second year across all treatment groups.

Withdrawals considered to be related to the study medications were higher in the combination group compared with each monotherapy group. The most frequently reported drug-related AE leading to withdrawal was erectile dysfunction, with similar incidence across the treatment groups.

Adverse Events of Special Interest

The following were defined as adverse events of special interest: altered libido, impotence, ejaculation disorders, prostate cancer and breast disorders. The incidence of impotence, altered libido and breast disorders were similar in both the combination and dutasteride only group, and slightly higher than in the tamsulosin group (Table 7). Ejaculation disorders were more common in the combination group than either monotherapy group. The incidence of prostate cancer was numerically lower in the dutasteride group compared with the combination and tamsulosin group. Few AEs of special interest were severe or led to premature withdrawal from the study.

Table 7: Incidence of Adverse Events of Special Interest (ITT population) - ARI40005

Composite AE Category	Number (%) Subjects					
	Combination N=1610		Dutasteride N=1623		Tamsulosin N=1611	
	Total	AE WD ^a	Total	AE WD ^a	Total	AE WD ^a
Ejaculation disorder	159 (10)	19 (1)	32 (2)	2 (<1)	49 (3)	9 (1)
Impotence ^b	132 (8)	21 (1)	118 (7)	13 (1)	73 (5)	13 (1)
Altered (decreased) libido	100 (6)	17 (1)	83 (5)	11 (1)	51 (3)	5 (<1)
Breast disorders	44 (3)	10 (1)	49 (3)	3 (<1)	21 (1)	3 (<1)
Breast tenderness	34 (2)	8 (1)	31 (2)	3 (<1)	12 (1)	1 (<1)
Breast enlargement ^c	23 (1)	7 (<1)	29 (2)	2 (<1)	13 (1)	2 (<1)
Prostate cancer	21 (1)	17 (1)	11 (1)	7 (<1)	26 (2)	21 (1)

- a. AE led to withdrawal
b. Category includes erectile dysfunction
c. Category includes gynecomastia

Most of the reports of altered libido, impotence and ejaculation disorders occurred in the first six months of treatment in each group, and diminished over time with the study. The mean onset time for impotence and ejaculation disorder was notably earlier in the combination group compared with either monotherapy. Onset of breast disorders was evenly distributed over time. The incidence of prostate cancer was low, and reported more frequently in all treatment groups during Year 2 compared to Year 1.

Combination therapy was associated with a significantly higher risk of ejaculation disorders compared with either monotherapy (Table 8). Relative to tamsulosin monotherapy, combination therapy was also associated with significantly higher risk of altered libido, impotence and breast disorders.

Table 8: Relative Risk Estimates for Adverse Events of Special Interest (ITT population) ARI40005

Composite AE Term	Relative risk estimate ¹ [95% CI]	
	Combination vs Dutasteride	Combination vs Tamsulosin
Altered (decreased) libido	1.23 (0.92, 1.65)	2.06 (1.46, 2.89) ***
Impotence	1.14 (0.89, 1.47)	1.87 (1.40, 2.48) ***
Ejaculation disorders	5.25 (3.59, 7.68) ***	3.47 (2.51, 4.79) ***
Prostate cancer	1.95 (0.94, 4.05)	0.82 (0.46, 1.46)
Breast disorders	0.91 (0.61, 1.37)	2.15 (1.28, 3.61) ***
Breast enlargement	0.81 (0.47, 1.39)	1.80 (0.91, 3.55)
Breast tenderness	1.12 (0.69, 1.81)	2.91 (1.51, 5.62) ***

AEs with onset on or after randomisation (or missing onset or treatment date).

*** Statistically significant; p-value versus combination based on log rank test

1. Relative risk (hazard ratio) based on Cox proportional hazards model

Cardiovascular AEs of special interest were defined as those included in the following categories: acute coronary syndrome, ischaemic coronary artery disorders/ atherosclerosis, ischaemic cerebrovascular events, cardiac failure, arrhythmias, and peripheral vascular disease. The incidence of cardiovascular AEs of special interest was similar across all three treatment groups, with the most frequently reported being myocardial infarction and coronary artery disease. Combination therapy was not associated with a significantly greater risk of cardiovascular AEs relative to either monotherapy. Although the relative risk of cardiac failure appears higher, the CIs cross zero and are relatively wide, reflecting the small numbers of patients with cardiac failure in each group.

Adverse Events in Special Groups

AE profiles in elderly patients (≥ 65 years of age) were generally similar to those in the younger patients in the study. Younger men reported a higher incidence of AEs related to sexual function across all treatment groups, which may reflect that a higher number of younger patients were sexually active.

Of the study population, 12% were non-White. There was a higher incidence of AEs in non-White patients in all three treatment groups (75-76%) compared with White patients (61-64%). In the combination group, most individual AEs were reported with a higher incidence by non-Whites than Whites.

Fifty percent of the study population reported concurrent cardiovascular conditions, and 21% reported concurrent endocrine disorders. There was no apparent difference in incidence or type of AEs in any treatment group noted between patients with and without these conditions.

The overall incidence of AEs in each treatment group was higher in patients using concomitant medications (cardiovascular drugs, endocrine and metabolic drugs, NSAIDs,

phosphodiesterase type V inhibitors, or quinolones) compared with those not using one of these medications. This was considered by the sponsor to be expected due to the increased risk of AEs associated with the underlying conditions and medications used to treat them and the evaluator agreed with this interpretation.

Laboratory Abnormalities, Vital Signs and Clinical Findings

The mean values for all haematology and clinical chemistry laboratory parameters were similar across the treatment groups at baseline, and Months 12 and 24. During this period, transitions in laboratory tests from baseline were similar across the treatment groups, with no consistent pattern being noted when comparing abnormalities. The proportion of patients with any parameter outside the pre-specified threshold was low and similar across the treatment groups (2% of patients). The majority of patients with threshold laboratory values had associated AEs, for example, diabetes and anaemia.

Baseline PSA and the corresponding baseline values for subjects with total PSA measurements at Months 12 and 24 were similar across the treatment groups. After Months 12 and 24 the mean PSA was consistently lower in the combination and dutasteride monotherapy group, compared to a small rise in the tamsulosin monotherapy group. The adjusted mean changes (reductions) from baseline in total PSA were significantly greater on combination therapy when compared to tamsulosin monotherapy at Months 12 and 24, whereas there was no statistical difference between combination and dutasteride monotherapy over time.

Assessment of gynaecomastia and digital rectal examinations (DREs) were conducted at baseline and at 6-month intervals. At baseline, 8% of patients in each treatment group had evidence of gynaecomastia. The incidence of post-baseline gynaecomastia was 8% in both the combination and dutasteride groups and in the tamsulosin group, it was 6%. A statistically significant higher proportion of patients in the combination group developed nipple tenderness compared to the tamsulosin group. The proportion of patients with an abnormal prostate on DRE clinically at baseline (2-3%) and at each 6-month interval up until Month 24 (1-2%) was low and similar across the treatment groups. There was no statistically significant difference between the combination and monotherapy groups in the proportion of patients who developed an abnormal prostate post baseline.

There were no clinically relevant trends noted in vital signs during the study. There was a similar proportion of patients with any baseline or post-baseline value outside the normal threshold across the treatment groups. The most frequently reported post-baseline threshold parameter was raised systolic blood pressure, and the incidence was similar across the treatment groups (14% in the combination group, 15% in each of the monotherapies).

Median changes in post void residual volume were significantly greater with combination therapy (-8.0 mL) compared to tamsulosin monotherapy (-1.0 mL) ($p < 0.001$). The reduction was also greater than with dutasteride alone (-4.0 mL), but statistical significance was not reached.

Supporting Studies - Study ARI40002

Drug Exposure and Overview of Adverse Events

A total of 421 patients were enrolled and entered the placebo run-in phase of this study, of which 94 discontinued prior to randomisation. The remaining 327 patients were randomised to receive either tamsulosin and dutasteride combination therapy for 36 weeks (TD36), or tamsulosin and dutasteride combination therapy for 24 weeks followed by dutasteride only for 12 weeks (TD24+D12). This comprised the ITT population for analysis.

During the first 24-week treatment period, the mean extent of exposure to study drug was similar between the treatment groups. The minimum exposure was 3 days, with this patient withdrawing prematurely due to an AE. During the final 12 weeks of the study, the median exposure was 84 days in both groups.

Overview of Adverse Events

During the first 24 week treatment phase, a total of 150 patients (46%) experienced 316 AEs, with a similar percentage in each treatment group experiencing an AE (TD36: 79 patients [48%], 159 events, TD24+D12: 71 patients [44%], 157 events). There were no clear differences between the treatment groups in the proportion of patients with an AE, or for specific AEs reported. Other than sexual function AEs (ejaculation disorders, impotence, altered libido), the only other AE reported in $\geq 5\%$ of patients was malaise and fatigue (Table 9). During the final 12 weeks of the treatment phase of the study, 32 patients (20%) who were maintained on combination therapy experienced 49 AEs, whereas in the group who received dutasteride only, 42 patients (26%) experienced 63 AEs. There were no clear differences between the groups.

Table 9: Summary of common adverse events ($>5\%$ of patients) occurring in ITT population.

Summary of Treatment-Emergent Adverse Events in $\geq 5\%$ of Subjects in Either Treatment Group
(Intent-to-Treat Population in Protocol ARI40002)

	TD36 Group (N=164)		TD24+D12 Group (N=163)	
	No. ^a	%	No. ^a	%
Week 0-24				
Any Adverse Event	79	48%	71	44%
Any Drug-related Adverse Event	45	27%	36	22%
Adverse Events in $\geq 5\%$ subjects:				
Ejaculation disorder	12	7%	12	7%
Altered (decreased) libido	7	4%	10	6%
Impotence	8	5%	4	2%
Malaise & fatigue	10	6%	3	2%
Week 24-36				
Any Adverse Event	32	20%	42	26%
Any Drug-related Adverse Event	11	7%	5	3%
Week 36-37				
Any Adverse Event	11	7%	9	6%
Week 37-52				
Any Adverse Event	13	8%	12	7%

^aRepresents the number of subjects reporting one or more adverse events

In total there were 156 AEs reported by 96 patients (29%) that were considered by the investigators to be drug-related (that is, having a reasonable possibility of being caused by the study medication). The incidence of drug-related AEs was similar between the treatment groups (Table 10). Events related to sexual function and malaise and fatigue were the most commonly reported drug related AEs.

Table 10: Summary of common (>5 patients) drug-related adverse events (ITT population)

**Summary of Drug-Related Adverse Events with Onset After Randomisation up to Week 37
in ≥5% of Subjects in Either Treatment Group
(Intent-to-Treat Population in Protocol ARI40002)**

	TD36 Group (N=164)		TD24+D12 Group (N=163)	
	No. ^a	%	No. ^a	%
Any Drug-related Adverse Event	54	33%	42	26%
Adverse Events in ≥5% subjects:				
Ejaculation disorder	14	9%	13	8%
Altered (decreased) libido	9	5%	10	6%
Impotence	9	5%	6	4%
Malaise & fatigue	8	5%	2	1%

^aRepresents the number of subjects reporting one or more adverse events

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

During the treatment phase of the study there were no deaths. However, during the follow-up period from Week 37 to Week 52 one patient died. He developed acute pulmonary oedema and cardiorespiratory arrest 27 days after his last dose of study medication. Review of the death narrative suggested that this death may not be related to the study medication due to his pre-existing cardiovascular disease and diabetes.

During the treatment phase of the study, 10 patients reported 13 SAEs. Of these, 7 were in the TD36 group and 3 were in the TD24+D12 group. The incidence of all SAEs was ≤1% and consisted mainly of cardiovascular events (for example, angina, arterial stenosis and arteriospasm) and gastrointestinal disorders (including herniae and obstruction). Only one SAE was considered by the investigators to have a reasonable possibility of being related to the study medication. A patient in the TD36 group developed chest pain and was found to have a pulmonary embolism. A further 7 AEs were reported during the follow up phase of the study, including the fatal AE described above. Four of these SAEs were experienced by 3 patients in the TD 36 group, and 3 experienced by 2 patients in the TD24+D12 group. None of these SAEs were considered by the investigators as being related to the study drug.

After randomisation, during the active treatment phase, there were a total of 21 AEs in 14 patients (TD36: 7patients/ 12 events, 4%; TD24+D12: 7 patients/ 9 events, 4%) which led to premature discontinuation of study medication. Of those patients who withdrew prematurely, 9 experienced 12 events which were considered by the investigators as having a reasonable possibility of being related to the study drug. With the exception of malaise and fatigue (which occurred in 2% in TD36 and <1% in TD24+D12), all other AEs leading to withdrawal occurred with frequency <1%.

Adverse Events of Special Interest

The AEs of special interest in the study included altered libido, impotence, disorders of sexual function, ejaculation disorders and gynaecomastia. The incidence of these AEs were comparable between the treatment groups and are summarised in Table 11. In the TD36 group, one subject was withdrawn for each of the events altered libido and impotence, and in the TD24+D12 group, one patient was withdrawn due to ejaculation disorder.

Table 11: Treatment Emergent AEs of Special Interest

Treatment-Emergent Adverse Events of Special Interest (Intent-to-Treat Population in Protocol ARI40002)								
	All Adverse Events				Drug-Related Adverse Events			
	TD36 Group (N=164)		TD24+D12 Group (N=163)		TD36 Group (N=164)		TD24+D12 Group (N=163)	
	No. ^a	%	No. ^a	%	No. ^a	%	No. ^a	%
Altered (decreased) libido	9	5%	11	7%	9	5%	10	6%
Impotence	9	5%	6	4%	9	5%	6	4%
Ejaculation disorders	14	9%	14	9%	14	9%	13	8%
Sexual function disorders	0	-	1	<1%	0	-	1	<1%
Gynaecomastia	1	<1%	0	-	1	<1%	0	-

^a Represents the number of subjects reporting one or more adverse events.

Altered libido was reported by 9 (5%) of patients in the TD36 group and by 11 (7%) in the TD24+D12 group. In all cases except for one in the TD24+D12 group, this was considered by the investigators to be related to the study medication. Median time to onset for altered libido was 29 days in the TD36 group and 46 days in the TD24+D12 group. At the time of the study report, altered libido had been noted to have resolved in 1/9 of patients in the TD36 group and in 2/11 patients in the TD24+D12 group.

Impotence was reported by 9 (5%) of patients in the TD36 group and 6 (4%) of the TD24+D12 group, and in all except the one case that withdrew in the TD36 group was reported as mild. The investigators considered all cases of impotence to be related to the study medication. Of these events, one case in the TD36 group resolved whilst still on the study medication, and two cases (one from each group) resolved off therapy.

Ejaculation disorders were reported by 14 (9%) of patients in the TD36 group and 14 (9%) in the TD24+D12 group. All reports were of mild-moderate intensity, and all except one case in the TD24+D12 group were considered by the investigators as being related to the study medication.

One patient in the TD24+D12 group reported a non-specific sexual function disorder of moderate intensity, which was considered by the investigators to be related to the study drug. The patient continued the study, and the disorder resolved off treatment.

One patient in the TD36 group reported gynaecomastia of mild intensity, which was considered by the investigators to be related to the study medication. Time to onset was 31 days, and at the time of the study report, this had remained unresolved.

There were two patients who reported one episode of AUR in the TD24+D12 group, which occurred during the treatment phase. One patient in each group required prostate surgery during the study period.

Laboratory Abnormalities, Vital Signs and Clinical Findings

The incidence of post-baseline laboratory values outside threshold was <1% for each analyte tested in both groups with the exception of alkaline phosphatase >1.5 the upper limit of normal (ULN) which occurred in 2 patients (1%). There was no statistical difference noted between the two groups.

The mean baseline PSA was 4.33 ng/mL (± 2.17) in the TD36 group and 4.33 ng/mL (± 2.21) in the TD24+D12 group. At week 36, in the TD 36 group, the mean PSA had decreased to 2.52 ng/mL (± 1.78) with an adjusted mean change of -1.8 ng/mL. In the TD24+D12 group

the mean PSA at Week 36 had decreased to 2.55 ng/mL (± 1.93), an adjusted mean change of -1.8 ng/mL.

Vital signs were comparable at baseline between the groups. During the treatment period there were 20% of patients in the TD36 group that had a measurement outside threshold, compared to 14% in the TD24+D12 group, with no statistically significant differences between the groups. Of patients that exceeded the upper systolic blood pressure threshold (<165 mmHg), 18% were in the TD36 group and 12% in the TD24+D12 group. There was no statistical difference, and generally these were single events with no obvious trends.

There was no significant change evident between the groups regarding evidence of gynaecomastia or changes in findings on DRE.

Supporting Studies - Study ARI40013

Drug Exposure and Overview of Adverse Events

A total of 2403 patients were screened, with 2385 patients being exposed at least once to the study medication. There were 1574 patients exposed to at least one dose of combination therapy with dutasteride 500 μ g + tamsulosin 400 mg (CT group) and there were 811 patients allocated to the dutasteride monotherapy group (MT). Duration of exposure to study medication was between 36 and 72 weeks.

Overview of Adverse Events

Adverse events occurring prior to first exposure to study medication were reported in 26 of the 2403 patients, 3 of which were not subsequently randomised. There were no pre-treatment SAEs reported. No statistical analysis of AE occurrence between the two groups is made, which the evaluator agreed was appropriate, given the non-matched nature of the treatment groups with regard to baseline disease characteristics.

A summary of the overall AEs occurring after the first dose of study medication is presented in Table 12. The incidence of AEs, SAEs and drug-related AEs was similar in both treatment groups, whereas the number of deaths was higher in the CT group. In the MT group, 303 patients (37.4%) reported any AE, compared to 613 patients (39.0%) in the CT group. The most commonly reported AEs (approximately 10% in each treatment group) were in the *Reproductive System and Breast Disorders* System Organ Class (SOC), and within this group the most frequently reported AEs by preferred terms were erectile dysfunction (4.4%), prostatitis (1.3%), retrograde ejaculation (1.3%), sexual dysfunction (0.8%) and gynaecomastia (0.6%) (Table 13). It was also noted that AEs in the class *Renal and Urinary Disorders* occurred more frequently in the CT group (108 patients, 6.9%) compared to the MT group (33 patients, 4.1%). This may well be due to the fact that patient allocated to the CT group had more severe disease at baseline (as evidenced by higher IPSS scores), and were therefore at higher risk of developing urinary AEs.

Table 12: Summary of overall treatment emergent adverse events (TEAEs) (ITT population) – ARI40013

	MT group N=811 n (%)	CT group N=1,574 n (%)	Total N=2,385 n (%)
Subjects with any TEAEs	303 (37.4%)	613 (39.0%)	916 (38.4%)
Subjects with non-fatal serious TEAEs	40 (4.9%)	78 (5.0%)	118 (5.0%)
Subjects with fatal serious TEAEs	1 (0.1%)	9 (0.6%)	10 (0.4%)
Subjects with serious TEAEs ^a	41 (5.1%)	87 (5.5%)	128 (5.4%)
Subjects with drug-related TEAEs	122 (15.0%)	279 (17.7%)	401 (16.8%)
Subjects with drug-related serious TEAEs	2 (0.3%)	4 (0.3%)	6 (0.25%)
Subjects with dutasteride-related serious TEAEs ^b	2 (0.3%)	3 (0.2%)	5 (0.2%)
Subjects with premature withdrawal due to AEs	59 (7.3%)	173 (11.0%)	232 (9.7%)

a No source, but the incidence of serious TEAEs could be calculated as the sum of subjects with non-fatal and fatal events, since no subjects with fatal TEAEs had previously experienced a non-fatal serious TEAE (ie, no overlapping events, cf. subject listings).

b Related to dutasteride alone or to both dutasteride and tamsulosin.

Note: No death was regarded as drug-related.

Note: "Drug-related" generally means a suspected relationship to dutasteride and/or tamsulosin (investigator's assessment).

Table 13: Overview of most common specified TEAEs within SOCs *Reproductive System and Breast Disorders* and *Renal and Urinary Disorders* by Preferred Term. (ITT population) – ARI40013

	MT group N=811 n (%)	CT group N=1,574 n (%)	Total N=2,385 n (%)
Reproductive system and breast disorders			
erectile dysfunction	38 (4.7%)	68 (4.3%)	106 (4.4%)
prostatitis	7 (0.9%)	24 (1.5%)	31 (1.3%)
retrograde ejaculation	4 (0.5%)	27 (1.7%)	31 (1.3%)
sexual dysfunction	6 (0.7%)	12 (0.8%)	18 (0.8%)
gynaecomastia	6 (0.7%)	8 (0.5%)	14 (0.6%)
Renal and urinary disorders			
dysuria	6 (0.7%)	40 (2.5%)	46 (1.9%)
urinary retention	5 (0.6%)	29 (1.8%)	34 (1.4%)
pollakiuria	3 (0.4%)	12 (0.8%)	15 (0.6%)
nocturia	3 (0.4%)	12 (0.8%)	15 (0.6%)
urge incontinence	2 (0.3%)	10 (0.6%)	12 (0.5%)

Note: Multiple answers per subject were possible.

Drug-related AEs were defined as those considered by the investigators to have a possible relationship to the study medication. There was a similar overall incidence between the treatment groups, with 122 patients (15.0%) in the MT group and 279 patients (17.7%) in the CT group experiencing AEs considered to be drug related. The most commonly reported drug-related AEs were related to sexual function and vegetative signs (for example, headache, fatigue, diarrhoea, hyperhidrosis, vertigo and nausea) and are summarised in Table 14.

Table 14: Drug-related AEs with an incidence of 0.5% or more in total population (ITT population) – ARI40013

	MT group N=811 n (%)	CT group N=1,574 n (%)	Total N=2,385 n (%)
Erectile dysfunction	31 (3.8%)	59 (3.8%)	90 (3.8%)
Retrograde ejaculation	4 (0.5%)	25 (1.6%)	29 (1.2%)
Headache	8 (1.0%)	18 (1.1%)	26 (1.1%)
Loss of libido	7 (0.9%)	19 (1.2%)	26 (1.1%)
Vertigo	2 (0.3%)	24 (1.5%)	26 (1.1%)
Fatigue	8 (1.0%)	13 (0.8%)	21 (0.9%)
Sexual dysfunction	4 (0.5%)	11 (0.7%)	15 (0.6%)
Gynecomastia	6 (0.7%)	8 (0.5%)	14 (0.6%)
Libido decreased	5 (0.6%)	9 (0.6%)	14 (0.6%)
Nausea	2 (0.3%)	11 (0.7%)	13 (0.6%)
Diarrhoea	4 (0.5%)	7 (0.4%)	11 (0.5%)
Hyperhidrosis	1 (0.1%)	10 (0.6%)	11 (0.5%)

Note: Multiple answers per subject were possible.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

There were 13 deaths during the treatment and follow up stages of the study, one in the MT group and 12 in the CT group. Of these, 10 occurred during the active treatment phase (one in the MT group, 9 in the CT group). None of these deaths were considered by the investigators as being possibly related to the study medication.

There were 118 patients (40 patients [4.9%] in the MT group and 78 patients [5.0%] in the CT group) who experienced SAEs. The overall rate of SAEs was similar between the two treatment groups. There were 8 patients that experienced AEs that were considered by the investigators as being possibly related to the study medication. Five of these were in the CT group (palpitations, atrial fibrillation, hyperbilirubinaemia, syncope and myocardial infarction) and three of them were in the MT group (raised blood pressure, peritoneal neoplasm, and gynaecomastia). Overall the analysis of the SAEs did not reveal any findings that would imply a re-assessment of the known risk-benefit profile of dutasteride.

There were 173 patients (11.0%) in the CT group and 59 patients (7.3%) in the MT group that withdrew from the study prematurely because of AEs. The AEs that most commonly led to withdrawal were dysuria and acute urinary retention, which occurred more frequently in the CT group compared to the MT group. The observed difference between the treatment groups in patients withdrawing in the CT group compared to the MT group, especially with regard to renal and urinary disorders, is potentially best explained by the increased severity of the disease at baseline in this group.

Adverse Events of Special Interest

There were no pre-defined AEs of special interest. There was an ad hoc analysis comparing AEs of special interest such as erectile dysfunction, altered libido, ejaculation disorders, breast disorders, BPH, urinary retention, prostate resection and prostate, pancreas or breast cancer between MT- and CT-treatment groups. It was found that these tended to occur earlier in the treatment period. Numerical differences between the treatment groups with a higher frequency of the ad hoc AE observed in the CT group were seen with urinary retention (1.7%

vs 0.5%), BPH symptoms (5.0% vs 2.7%), ejaculation disorders (2.9% vs 1.2%) and prostate cancer (0.4% vs 0.0%). There were no reports of breast or pancreatic cancer.

Laboratory Abnormalities, Vital Signs and Clinical Findings

Laboratory values were recorded at baseline for all patients, but were only recorded at the end if there were any clinically significant abnormal values or changes from baseline.

Consequently, post-baseline documentation of laboratory values was reported as being scarce. Generally analysis of laboratory values did not indicate any clinically relevant or unexpected risk associated with the study medication.

There were no noteworthy changes in heart rate or blood pressure during the study period

Safety Conclusions

A total of 3511 patients were treated with combination therapy with dutasteride 500 µg once daily and tamsulosin 400 mg once daily across the three studies evaluated. Combination therapy was well tolerated, for up to two years in the pivotal study ARI40005.

In the pivotal study ARI40005, the overall incidence of adverse effects was similar in the combination therapy and monotherapy groups.

The incidence and type of adverse events occurring whilst on combination therapy in all three studies were consistent with the already known safety profiles of dutasteride and tamsulosin.

The most commonly reported AEs considered to be drug-related were related to sexual function, especially ejaculation disorders, which occurred more commonly with combination therapy compared to either monotherapy.

Incidence of SAEs was similar across the treatment groups and the most frequently reported were cardiovascular disorders.

There was no significant adverse trend in vital signs, clinical findings or laboratory values in any of the studies.

Post-marketing Experience

At the time of the submission, the Duodart DTC had not yet been marketed anywhere worldwide, and so there was no post-marketing experience with the specific product. However there has been experience with co-administration of dutasteride and tamsulosin.

The sponsor examined their own GSK world-wide safety database OCEANS (Operating Companies Event Accession and Notification System), and two publicly available external post-marketing safety databases, FDA Adverse Event Reporting System (AERS) and the World Health Organization (WHO) Vigibase, for information regarding the combined use of dutasteride and tamsulosin.

As of 31 August 2009, GSK OCEANS had received 580 spontaneous reports detailing a total of 1344 AEs containing dutasteride as a suspect or concomitant drug, and tamsulosin as a suspect or concomitant drug. The most frequently reported events were drug ineffective (79 events), dysuria (35 events), erectile dysfunction (29 events), gynaecomastia (29 events), dizziness (22 events), rash (22 events), breast tenderness (21 events), pollakiuria (20 events), decreased libido (20 events) and fatigue (20 events).

The FDA AERS contained 526 reports containing both dutasteride and tamsulosin, and Vigibase contained 185 reports containing both dutasteride and tamsulosin.

Disproportionality analysis using these databases revealed no adverse events unique to the combination of dutasteride with tamsulosin; the events reported with high frequency when dutasteride and tamsulosin were co-reported are consistent with the known safety profile or

pharmacological activity of either dutasteride, tamsulosin, or the clinical effects of the underlying BPH.

Clinical Summary and Conclusions

Duodart is a combination preparation containing dutasteride 500 µg and tamsulosin 400 µg which has been submitted for registration for the indication of “treatment and prevention of the progression of BPH in patients with an enlarged prostate, to reduce prostate size, alleviate symptoms, improve urinary flow and reduce the risk of acute urinary retention and the need for BPH-related surgery”

Bioequivalence data submitted show that the Duodart DTC capsule delivers the same dutasteride and tamsulosin exposure as co-administration. Therefore, efficacy and safety data from the co-administration study ARI40005 can be extrapolated to describe the effects of the DTC capsule.

Data from all three studies evaluated would support the efficacy of DTC in the improvement of symptoms in patients with BPH. Data from the pivotal study ARI40005 demonstrated that combination therapy with dutasteride and tamsulosin was significantly better at improving symptoms as evidenced by change in IPSS than either drug used as monotherapy. Also urinary flow rates were demonstrated to be significantly improved with combination therapy compared to either monotherapy. Reduction in prostate volume was similar when treated with either combination therapy or dutasteride alone, with either being superior to monotherapy with tamsulosin.

However, the evaluator believed that there has not been sufficient evidence presented by the sponsor for reduction of episodes of acute urinary retention, or the reduction in need for surgery related to BPH with the combination tablet (Duodart).

The safety profile of co-administration was favourable, with the nature and frequency of AEs reported in all three studies being consistent with the safety profiles of either monotherapy. The most frequently reported drug-related AEs were related to sexual function (impotence, altered libido, ejaculation disorders), and ejaculation disorders were more commonly reported with combination therapy.

On balance of its demonstrated clinical efficacy, the statistically and clinically significant improvement in symptoms compared to either monotherapy, the favourable safety profile, and the potential compliance benefits gained from a single capsule formulation, the evaluator recommended approval to register Duodart for the indication “treatment and prevention of the progression of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate, to reduce prostate size, alleviate symptoms and improve urinary flow.” However, more evidence was required before Duodart can be approved for indications relating to reduction of the risk of acute urinary retention and reduction in the need for BPH-related surgery.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA’s Office of Medicines Safety Monitoring (OMSM).

The ongoing safety concerns were identified by the sponsor as follows:

Important identified risks:

- Sexual adverse events (altered [decreased] libido, impotence, ejaculation disorders) and breast disorders (enlargement and tenderness)
- Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema

- Orthostasis signs and symptoms
- Intraoperative Floppy Iris Syndrome (IFIS)

Important potential risks:

- Male breast cancer
- Cardiovascular Events
- High-grade prostate cancer
- Interference with formation of external male genitalia in the foetus
- Priapism

Important missing information:

- Men with severe hepatic impairment
- Men with unstable medical conditions

A number of unexpected inconsistencies between the latest versions of the Safety Specifications (Part I) of the RMPs for Duodart and Avodart were noted. The latter document was submitted in support of an application to extend the approved indications for Avodart to include combination therapy with an alpha-blocker (tamsulosin).¹⁷

The sponsor advised that this was an artefact of a number of Category 1 applications associated with these medicines having been submitted simultaneously to the TGA. Given that these documents are essentially similar, it was recommended that these documents be revised and/or updated by the sponsor to be consistent with each other.

In principle there was no objection to the sponsor implementing the proposed application of routine pharmacovigilance activities for all the specified ongoing safety concerns and the application of additional pharmacovigilance activities for 'IFIS', 'Male breast cancer', 'Cardiovascular events', 'High-grade prostate cancer' and 'Interference with formation of external male genitalia in the foetus'.²⁵ The sponsor provided an assurance that updates will be provided in Periodic Safety Update Reports (PSURs), unless a significant safety issue emerges requiring more immediate notification to regulatory authorities. This was considered acceptable. Nevertheless the OMSM reviewer indicated that the sponsor should provide a copy of the targeted follow-up questionnaire specific to breast cancer and a copy of the targeted follow-up questionnaire specific to cardiovascular adverse events to the TGA.

In addition, the current RMP for Avodart states that a targeted follow-up questionnaire is used to request additional information on spontaneous reports of prostate cancer. This questionnaire asks for results of diagnostic tests (including PSA, biopsy results, histopathology data), medical history, family history, risk factors for prostate cancer, treatment, and details about dutasteride use (that is, when dutasteride was started and time to onset of the cancer). It was suggested that this additional pharmacovigilance activity be included in the RMP for Duodart and a copy of the targeted follow-up questionnaire used to

²⁵ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

request additional information on spontaneous reports of prostate cancer be provided to the TGA.

Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns, except for 'Cardiovascular events', 'High-grade prostate cancer' and 'Men with unstable medical conditions'.²⁶ This was considered generally acceptable. However, the absence of any routine risk minimisation activities for the important potential risks: 'Cardiovascular events' and 'High-grade prostate cancer' contradicts the information in the current RMP for Avodart.

Recommendations were also made with respect to the proposed PI but these are beyond the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Details of this submission were presented at the 132nd meeting of the PSC in May 2010. The PSC had reservations regarding the tradename and the large difference in the elimination half-lives of dutasteride and tamsulosin. Approval was conditionally recommended from a quality perspective (subject to provision of some dissolution specifications). There was satisfactory demonstration of bioequivalence of Duodart to Avodart and to US Flomax (Study ARI109882). Bioequivalence was also demonstrated between Flomax and Omnic MR (Study ARI10021). As the pharmaceutical chemistry evaluator noted, the justification for not providing biopharmaceutic data assessing the bioequivalence of the tamsulosin component of Duodart to the Australian-registered Flomaxtra will require clinical assessment. The Delegate noted with interest the potential for dose-dumping of tamsulosin if large quantities of ethanol are imbibed prior to the meal consumed before administration of the Duodart capsule. The sponsor was required to provide a detailed comment about this issue in its pre-ACPM response and also indicate how this will be managed in the PI and CMI.

Nonclinical

Nonclinical studies using a combination of dutasteride and an alpha blocker were not submitted. New data were primarily limited to secondary and safety pharmacology studies with the individual components.

New data showed that dutasteride:

- has little affinity for a wide range of other steroid receptors (androgen, glucocorticoid, mineralocorticoid and progesterone)
- has moderate passive cellular membrane permeability, and
- is unlikely to have any significant effect on CYP enzymes, organic anion transporters or multidrug resistance proteins at clinically relevant plasma concentrations.

New data for tamsulosin confirmed its high affinity for the human alpha-1_a adrenergic receptor (with moderate affinity for the 1_b and 1_d sub-types) and showed that it had low

²⁶ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

affinity for the hERG channel (IC_{50} of 105 μ M, 3000 times the C_{max} for tamsulosin after a 400 mg clinical dose).

Consistent with the TGA-adopted EU guideline on the non-clinical development of fixed combinations of medicinal products, the results support the specificity of dutasteride and tamsulosin and suggest that the potential for undesirable pharmacodynamic, pharmacokinetic or toxicological interactions following co-administration is low.¹⁹

The nonclinical evaluator was of the opinion that the sponsor had provided an acceptable justification for the absence of non-clinical combination studies by reference to the TGA-adopted EU guideline and consideration of extensive clinical experience with co-administration of the products. Also the nonclinical profiles of both dutasteride and tamsulosin have been previously reviewed by the TGA and other international regulatory agencies and have been expanded by the new data contained in the current submission.

The nonclinical evaluator concluded that the weight of nonclinical evidence suggests that the potential for adverse pharmacodynamic, pharmacokinetic or toxicological interactions with Duodart is low. Therefore there were no objections, on nonclinical grounds, to the registration of Duodart for the treatment of benign prostatic hyperplasia and acute urinary retention.

Clinical

The clinical data comprised the following studies:

- six studies relating specifically to the clinical pharmacology of Duodart, the fixed-dose combination capsule containing dutasteride 500 μ g and tamsulosin 400 mg (there was also a seventh study, ARIA 1011, common to both Duodart and Avodart submissions).
- 3 Phase III clinical efficacy and safety studies of the co-administration of dutasteride and tamsulosin – Study ARI40005 was a pre-determined interim 2-year analysis of a 4-year pivotal study; Studies ARI40002 and ARI40013 were supporting studies.

Tamsulosin was selected as the alpha blocker of choice for co-administration because there is no need for dose titration, it has a more favourable safety profile compared with other alpha blockers and there are no known PK/PD interactions between dutasteride and tamsulosin.

The clinical evaluator recommended approval for a somewhat modified indication compared with the one proposed by the sponsor. This modified indication reads as follows:

Duodart is indicated for the treatment and prevention of the progression of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate, to reduce prostatic size, alleviate symptoms and improve urinary flow.

As there was no data in the submission to support efficacy of the combination tablet (Duodart) for the reduction of risk of developing acute urinary retention or for the reduction of the need for BPH-related surgery, the clinical evaluator recommended that the latter not be included in the indication and thus recommended the shortened version.

Pharmacology

ARI109882 was an open-label, randomised, single dose, three-period, partial crossover study which examined the bioequivalence and food effect of a combination capsule formulation of dutasteride and tamsulosin (500 μ g/ 400 mg) compared to concomitant dosing of separate Avodart 500 μ g and Flomax 400 mg in the fasted and fed state. Fasting or feeding before administration in the presence or absence of 400 mg tamsulosin had little effect on the C_{max} and AUC of dutasteride. Dutasteride T_{max} values were also essentially equivalent between

regimens. By contrast, the C_{\max} values of tamsulosin for both fed regimens were found to be approximately 30% less than both fasted regimens. Thus food affected both the test and the reference dosage forms in a similar way. There was no significant difference between regimens with regard to T_{\max} .

ARI111402 was an open-label, randomised, repeat dose, 3 period crossover study which examined the bioequivalence with regard to tamsulosin pharmacokinetics of 2 different test formulations of the dutasteride and tamsulosin combination capsule (one 10 % enteric coated and the other 15% enteric coated) versus the reference free combination of dutasteride (Flomax 400 mg) and tamsulosin (Avodart 500 µg), given concomitantly. Each of the test formulations was shown to be bioequivalent to the reference formulation with respect to tamsulosin PK parameters. The effect of the different formulations on dutasteride pharmacokinetics was not examined in this study.

Capmul MCM (glyceryl mono- and di-caprate) is an emulsifying agent used in the production of the capsules. ARI103880 examined the bioequivalence of dutasteride 500 µg in soft gelatine capsules containing 350 mg of Capmul MCM (Avodart, reference) versus two test formulations with the same amount of dutasteride in soft gelatine capsules but with varying amounts of Capmul MCM, 300 mg and 100 mg. The comparisons for both AUC_{0-72} and C_{\max} were almost all contained within the standard interval of [80%, 125%], the one exception being that for the comparison of test (capsule with 100 mg Capmul MCM) versus reference (Avodart with 350 mg Capmul MCM) for C_{\max} . Here the lower limit of the 90% CI was 0.79. There was a trend to a lesser C_{\max} with progressively lesser amounts of Capmul MCM. None of these results was of clinical significance.

163/07 Sython Pilot 1 and 186/07 Sython Pilot II were studies which compared two different test formulations of tamsulosin 400 mg modified release with the same reference product, Flomax 400 mg modified release capsules. In each case, the 90% CIs for the test to reference ratios of the geometric least squares means for the tamsulosin PK parameters were all well within the prescribed limits of [80%, 125%].

ARI10021 was an open-label, single dose, 2-way crossover study which established the bioequivalence of Flomax (tamsulosin 400 mg capsule, USA) and Omnic (tamsulosin 400 mg capsule, Germany).

The sponsor did not submit any clinical data testing bioequivalence between the tamsulosin component of the proposed fixed-dose combination product, Duodart and the currently marketed tamsulosin product in Australia, FlomaxTRA. The former is a modified release formulation contained within a hard capsule whereas the latter is a prolonged-release film-coated tablet. The sponsor did submit a clinical justification for not submitting such data. The Delegate requested the sponsor to provide copies of the published papers which supported this justification.

The pharmacology of dutasteride was evaluated in a Phase I alpha blocker – dutasteride interaction study (ARIA 1011), completed in January 1999. This randomized, open-label, single-sequence, 56-day crossover study in 48 healthy volunteers assessed the PD/PK interactions between dutasteride and either of the alpha blockers, tamsulosin or terazosin. There were the following findings:

- Similar DHT suppression was observed with dutasteride alone compared with the combination treatments with either alpha blocker. Similar trough concentrations of dutasteride were observed during combination treatment with either alpha blocker.

- Dutasteride 500 µg had no effect on the steady state pharmacokinetics of tamsulosin 400 mg or terazosin titrated to 10 mg. In addition, similar DHT suppression was observed with dutasteride alone compared to the combination treatment with either alpha blocker. Similar trough concentrations of dutasteride were observed during combination treatment with both alpha blockers.

ARIA 1011 showed that dutasteride does not affect the pharmacokinetics of tamsulosin. However, the effects of tamsulosin on the pharmacokinetics of dutasteride were not evaluated in this study. In addition to the data from ARIA 1011, the metabolic pathways for dutasteride and tamsulosin as well as the exposure levels for dutasteride were examined for any evidence that would support a clinically significant interaction between these two compounds.

Dutasteride is metabolized by the CYP3A4/5 isoenzymes. Available literature supplied by the sponsor and the approved PI for tamsulosin indicate that tamsulosin does not inhibit CYP3A4, 2C9 or 2D6, making a drug interaction with dutasteride unlikely. *In vitro* studies with human liver microsomes show that CYP3A4 and CYP2D6 are the predominant enzymes responsible for tamsulosin metabolism. There are no time-dependent changes in the pharmacokinetics of tamsulosin with multiple dosing, making it unlikely that tamsulosin induces any of the isoenzymes responsible for its metabolism. From the studies included in the dossier for initial registration, dutasteride has been demonstrated to have a wide safety margin.

Efficacy

Data which support the efficacy of co-administration of dutasteride and tamsulosin come from the pre-defined 2-year analyses of the pivotal 4-year study, ARI40005 and from two supporting studies, ARI40002 and ARI40013.

Pivotal Study ARI40005 (CombAT – Combination with Alpha-blocker Therapy)

ARI40005 was the Phase III study designed to demonstrate the superiority of combination therapy of dutasteride 500 µg and tamsulosin 400 mg over dutasteride 500 µg or tamsulosin 400 mg alone. It was a multicentre, randomized, double-blind, parallel-group study of the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic BPH and it consisted of a 4-week single-blind placebo run-in period, a 4-year double-blind treatment period and a 16-week safety follow-up period.

The primary efficacy endpoint at Year 2 was change from baseline in the International Prostate Symptom Score (IPSS) and the primary comparisons of interest for this parameter were the combination therapy versus each monotherapy. For IPSS, the hypothesised superiority of combination therapy over dutasteride monotherapy was 1.5 units and for tamsulosin monotherapy was 1.0 unit. Comparable efficacy gains versus placebo have been demonstrated for finasteride, tamsulosin and alfuzosin.

Key Year 2 secondary endpoints included change from baseline in prostate volume (PV), peak urinary flow rate (Q_{max}), BPH Impact Index (BII), BPH-related health status (question 8 of the IPSS, also known as IPSS-QOL) as well as the proportions of subjects with IPSS improvement from baseline of ≥ 2 units, ≥ 3 units and $\geq 25\%$ and the proportions of subjects with Q_{max} improvements from baseline of $\geq 30\%$ and ≥ 3 mL/sec.

Primary efficacy results: At 24 months, a statistically significantly greater reduction (improvement) from baseline in IPSS was achieved with combination therapy compared with either dutasteride or tamsulosin monotherapy. The hypothesised superiority margin of 1.5 units of combination therapy over dutasteride monotherapy was met in the At Visit analysis

(but not in the LOCF analysis) and that of 1.0 unit over tamsulosin was satisfied in both At Visit and LOCF analyses. These results are shown in Table 4.

Reductions from baseline in IPSS were consistently numerically greater with combination therapy compared with either monotherapy and were continued over 24 months. These differences were statistically significant between combination therapy and dutasteride beginning at Month 3 and between combination therapy and tamsulosin beginning at Month 9. These results are shown in Table 15 which also shows the plateauing of the differences between the results for the combination and dutasteride monotherapy groups and the gradual widening of the differences between the results of the combination and tamsulosin monotherapy groups. These trends reflect the differences in physiological action and time to onset of action of dutasteride and tamsulosin.

Table 15: Change from baseline in IPSS (LOCF and At Visit), ITT population - ARI40005

Time Point	Adjusted mean change from baseline (SE)					
LOCF	N	Combination	N	Dutasteride	N	Tamsulosin
Month 3	1564	-4.8 (0.14)	1582	-2.8 (0.14)	1573	-4.5 (0.14)
Month 9	1575	-5.4 (0.14)	1592	-4.0 (0.14)	1582	-4.7 (0.14)
Month 12	1575	-5.6 (0.15)	1592	-4.2 (0.15)	1582	-4.5 (0.15)
Month 24	1575	-6.2 (0.15)	1592	-4.9 (0.15)	1582	-4.3 (0.15)
At Visit	N	Combination	N	Dutasteride	N	Tamsulosin
Month 3	1541	-4.8 (0.14)	1570	-2.8 (0.14)	1562	-4.5 (0.14)
Month 6	1471	-5.0 (0.14)	1509	-3.5 (0.14)	1507	-4.5 (0.14)
Month 12	1389	-6.0 (0.15)	1426	-4.5 (0.15)	1429	-4.7 (0.15)
Month 24	1258	-6.8 (0.15)	1287	-5.3 (0.15)	1237	-5.0 (0.16)
LOCF	Adjusted mean difference of combination from monotherapy (SE) [95% CI]					
	Dutasteride		P-value ¹	Tamsulosin		P-value ¹
Month 3	-2.0 (0.192) [-2.33, -1.57]		<0.001	-0.26 (0.192) [-0.63, 0.12]		0.18
Month 9	-1.4 (0.199) [-1.79, -1.01]		<0.001	-0.74 (0.199) [-1.13, -0.35]		<0.001
Month 12	-1.4 (0.202) [-1.80, -1.01]		<0.001	-1.1 (0.203) [-1.53, -0.73]		<0.001
Month 24	-1.3 (0.212) [-1.69, -0.86]		<0.001	-1.8 (0.212) [-2.23, -1.40]		<0.001
At Visit	Dutasteride		P-value ¹	Tamsulosin		P-value ¹
Month 3	-2.0 (0.191) [-2.37, -1.62]		<0.001	-0.31 (0.191) [-0.68, 0.07]		0.11
Month 6	-1.5 (0.195) [-1.89, -1.12]		<0.001	-0.51 (0.195) [-0.90, -0.13]		0.009
Month 12	-1.5 (0.205) [-1.92, -1.11]		<0.001	-1.3 (0.205) [-1.68, -0.88]		<0.001
Month 24	-1.5 (0.215) [-1.93, -1.08]		<0.001	-1.9 (0.217) [-2.28, -1.43]		<0.001

1. p-values based on t-tests from the general linear model

Selected key secondary endpoints: Changes (increases) in peak urinary flow rate, Q_{max} , from baseline were consistently higher on combination therapy compared with either monotherapy at each 6 month assessment up to 24 months. These results are seen in Table 16.

Table 16: Change from baseline in Q_{max} (LOCF) – ARI40005

Time Point	Adjusted mean change from baseline (SE)					
	N	Combination	N	Dutasteride	N	Tamsulosin
Month 6	1388	2.0 (0.12)	1406	1.2 (0.12)	1445	1.2 (0.11)
Month 12	1477	2.0 (0.12)	1483	1.5 (0.12)	1510	0.9 (0.12)
Month 18	1487	2.3 (0.12)	1496	1.8 (0.12)	1517	1.1 (0.12)
Month 24	1492	2.4 (0.12)	1502	1.9 (0.12)	1519	0.9 (0.12)
	Adjusted mean difference of combination from monotherapy (SE) [95% CI]					
	Dutasteride		P-value ¹	Tamsulosin		P-value ¹
Month 6	0.75 (0.162) [0.43, 1.06]		<0.001	0.78 (0.161) [0.46, 1.09]		<0.001
Month 12	0.50 (0.164) [0.17, 0.82]		0.002	1.12 (0.163) [0.80, 1.44]		<0.001
Month 18	0.47 (0.172) [0.14, 0.81]		0.006	1.23 (0.171) [0.90, 1.57]		<0.001
Month 24	0.51 (0.172) [0.17, 0.84]		0.003	1.52 (0.172) [1.19, 1.86]		<0.001

Source: Table E9

1. P-values based on t-tests from the general linear model

At Month 24, a statistically significantly greater proportion of subjects treated with combination therapy had IPSS improvements of ≥ 2 units, ≥ 3 units and $\geq 25\%$ from baseline compared with either monotherapy. Compared with dutasteride monotherapy, these improvements were sustained from Month 3, while compared with tamsulosin monotherapy, these improvements were sustained from Month 9. These results are shown in Table 17.

Table 17: IPSS changes from baseline – improvement categories tested for significance (LOCF) - ARI40005

Time point Improvement category	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	p-value ¹	Tamsulosin N=1611 n (%)	p-value ¹
Month 3	N=1564	N=1582		N=1573	
≥2 units	1132 (72)	935 (59)	<0.001	1109 (71)	0.24
≥3 units	1015 (65)	824 (52)	<0.001	1000 (64)	0.42
≥25%	888 (57)	654 (41)	<0.001	851 (54)	0.12
Month 6	N=1572	N=1591		N=1581	
≥2 units	1139 (72)	997 (63)	<0.001	1102 (70)	0.082
≥3 units	1040 (66)	884 (56)	<0.001	988 (62)	0.029
≥25%	914 (58)	746 (47)	<0.001	868 (55)	0.060
Month 9	N=1575	N=1592		N=1582	
≥2 units	1170 (74)	1053 (66)	<0.001	1104 (70)	0.004
≥3 units	1082 (69)	958 (60)	<0.001	1006 (64)	0.002
≥25%	979 (62)	835 (52)	<0.001	912 (58)	0.009
Month 24	N=1575	N=1592		N=1582	
≥2 units	1207 (77)	1121 (70)	<0.001	1078 (68)	<0.001
≥3 units	1128 (72)	1027 (65)	<0.001	980 (62)	<0.001
≥25%	1054 (67)	934 (59)	<0.001	876 (55)	<0.001

1. P-value based on a Mantel-Haenszel test controlling for cluster

Consistent changes in all the other secondary endpoints were observed in favour of the combination therapy compared with either of the monotherapies.

Non-pivotal trials - Study ARI40002

This was a short-term, pilot, multi-centre, double-blind, parallel group randomised study to investigate the effect on urinary symptoms of discontinuing tamsulosin, following 24 weeks of combination treatment with 500 µg dutasteride and 400 mg tamsulosin daily in subjects with BPH. Patients were randomised in a 1:1 ratio to receive either 36 weeks of combination therapy with dutasteride 500 µg daily and tamsulosin 400 mg daily (TD36 group) or 24 weeks of combination therapy followed by 12 weeks of dutasteride 500 µg daily monotherapy (TD24 + D12 group). The last 12 weeks of the study were performed in a double-blind manner.

The primary objective was to assess any difference at 30 weeks post baseline in the proportions of patients experiencing an improvement or no change in their urinary symptoms following discontinuation or continuation of tamsulosin. The study was designed as a non-inferiority study such that if the lower bound of the 97.5% CI for the difference in proportions was less negative than -0.20, then non-inferiority could be claimed.

At Week 30, 91% (139/154) patients who continued combination therapy after 24 weeks (TD36 group), felt the same or better regarding urinary symptoms than at the previous visit. In the group who discontinued tamsulosin after Week 24 (TD24 + D12 group), 77% (115/151) felt the same or better than at the previous visit. The point estimate for the difference in these proportions was -0.11 with a corresponding CI of [-0.18, -0.04]. As the lower bound, -0.18, was less negative than -0.20, non-inferiority between the two treatments was demonstrated.

Study ARI40002 also demonstrated that once tamsulosin was stopped after 24 weeks, patients, over the following 6 weeks, had an increase in their symptom score that was

statistically significantly higher than that for the patients who continued on combination therapy.

Non-pivotal trials - Study ARI40013

This was an open-label, multicentre, Phase IIIb study to evaluate the safety and efficacy of dutasteride with or without tamsulosin in the treatment of a large cohort of patients with symptomatic BPH under routine clinical conditions. If the baseline IPSS-QOL score was < 4 points they were to receive monotherapy with dutasteride 500µg once daily [monotherapy group, MT]. If the baseline IPSS-QOL score was 4 points or more, they were to receive combination therapy with dutasteride 500µg once daily plus tamsulosin 400 mg once daily for 24 weeks, followed by dutasteride monotherapy for the remaining 12 weeks [combination therapy group, CT]. Of the 2385 patients considered eligible for participation, 811 were assigned to the MT group and 1574 to the CT group, these numbers being in accord with the expected ratio of 1:2 (MT:CT), according to baseline severity.

The primary efficacy outcomes of interest were the changes in IPSS and BII from baseline to Week 36 of the study. At Week 36, both the treatment groups showed reductions in the primary efficacy variables. In the monotherapy group, the mean total IPSS had changed by -5.1, 95% CI [-5.4, -4.7] and the mean BII by -2.3, 95% CI [-2.5, -2.1]. In the combination group, the corresponding changes were, for the IPSS, -7.1, 95% CI [-7.4, -6.7] and for the BII score, -2.3, 95% CI [-3.6, -3.3].

As acknowledged in the submission and noted by the evaluator, the larger mean reduction in IPSS in the CT group compared with that in the MT group, was most likely explained by the patients in the CT group having started from higher baseline values, indicative of worse symptoms. On the basis of the latter and also because of the open-label design and the absence of any formal, pre-defined statistical comparison, the evaluator recommended that no conclusions could be drawn from this study relating to an increased benefit of combination therapy compared to monotherapy. While the Delegate agreed with this, it was reassuring that the results of this study are consistent with those of the pivotal study. The evidence adduced from this study is therefore supportive.

Safety

As noted by the clinical evaluator:

- A total of 3511 patients were treated with combination therapy with dutasteride 500 µg once daily and tamsulosin 400 mg once daily across the three studies, ARI40005, ARI40002 and ARI40013. Combination therapy was well tolerated, for up to two years in the pivotal study, ARI40005.
- In the pivotal study ARI40005, the overall incidence of adverse effects was similar in the combination therapy and monotherapy groups.
- The incidences and types of adverse events occurring whilst on combination therapy in all three studies were consistent with the already known safety profiles of dutasteride and tamsulosin.
- The most commonly reported adverse events considered to be drug-related were related to sexual function, especially ejaculation disorders, which occurred more commonly with combination therapy compared to either monotherapy.
- The incidence of SAEs was similar across the treatment groups and the most frequently reported were cardiovascular disorders. In the pivotal study,

cardiovascular AEs of special interest were defined as those in the following categories: acute coronary syndrome, ischaemic coronary artery disorders/atherosclerosis, ischaemic cerebrovascular events, cardiac failure, arrhythmias and peripheral vascular disease. The incidence of cardiovascular AEs of special interest was similar across all three treatment groups, with the most frequently reported being myocardial infarction and coronary artery disease. Combination therapy was not associated with a significantly greater risk of cardiovascular AEs relative to either monotherapy.

- It was noted that the relative risk of cardiac failure appeared higher, with a 4.54-fold higher risk in the combination group relative to the dutasteride monotherapy group and a 2.29-fold higher risk in the combination group relative to the tamsulosin monotherapy group. While the associated confidence intervals do include unity and are relatively wide, reflective of the small numbers of events involved, they do stand out somewhat in relation to the relative risk estimates for the other cardiovascular AEs of special interest.
- There were no significant adverse trends in vital signs, clinical findings or laboratory values in any of the studies.

At the time of the submission, the Duodart DTC capsule had not yet been marketed anywhere worldwide. With respect to post-marketing experience for the combined use of the free monotherapies, dutasteride and tamsulosin, the sponsor submitted data gleaned from four primary sources, the public literature, GSK's own world-wide safety data base OCEANS (Operating Companies Event Accession and Notification System) and two publicly available external post-marketing safety databases, the FDA Adverse Event Reporting System (AERS) and the World Health Organisation (WHO) Vigibase. As noted by the evaluator, various analyses, including disproportionality analyses did not reveal any adverse events unique to the combination of dutasteride and tamsulosin. The high frequency adverse events reported with the concomitant use of dutasteride and tamsulosin were consistent with the known safety profile or pharmacological activity of either of the two drugs or the clinical effects of the underlying BPH.

Other Data/Issues

Incidence of heart failure on the combination therapy compared with that on each monotherapy

In August 2009, the sponsor submitted another category 1 application, PM-2009-02487-3-3, to update the Clinical Trials and Precautions sections of the PI for Avodart (dutasteride) with particular information about cardiac failure from the 4-year results of two studies, the first being the pivotal study for this submission, ARI40005 (note that in this submission, the 2-year results of ARI40005 or CombAT have been submitted) and the second being a study named REDUCE, a 4-year comparison of placebo and dutasteride in men at risk of developing prostate cancer. In these two 4-year clinical studies, the incidence of cardiac failure was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. As previously noted, this closely related submission was being evaluated at around the same time as the current submission.¹⁷

With regard to the issue of cardiac failure, in section 5.2, Pharmacodynamic properties, of the EU Summary of Product Characteristics (SmPC) documents for both Avodart (dutasteride) and the combination Combodart (dutasteride and tamsulosin), there is the following entry under the heading Cardiac failure:

In this 4 year BPH study the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: Avodart, (4/1623, 0.2%) and tamsulosin, (10/1611, 0.6%)”.

Reference to this finding about cardiac failure is repeated in the second paragraph of section 4.4, Special warnings and precautions for use. The reporting is qualified by the fact that no causal relationship between Avodart (alone or in combination with an alpha blocker) and cardiac failure has been established.

Justification for not submitting biopharmaceutic data

This submission for Duodart consists of a Phase III efficacy and safety study (CombAT) and a series of bioequivalence studies which demonstrate bioequivalence between the individual components in Duodart and the versions of dutasteride (500 µg) and tamsulosin (400 mg) which were used in the pivotal co-administration study, ARI40005 (CombAT)²⁷. However, according to Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), the sponsor is also required to demonstrate bioequivalence of the active ingredients in the fixed combination product to each of the components administered separately as registered formulations, that is, as formulations registered here in Australia.

As pointed out by the sponsor, the global product development of Duodart and the choice of tamsulosin comparator in the CombAT study were based upon the most commonly used formulation of tamsulosin available at the time. Since this initial stage in the development of Duodart, the innovator formulation of tamsulosin has changed to a new prolonged release formulation, the oral-controlled absorption system (OCAS). No further bioequivalence work has been conducted following this change in the marketed tamsulosin product. Therefore the sponsor does not have available any data which tests the bioequivalence between the tamsulosin component of the fixed-dose combination proposed for registration, Duodart and the currently marketed innovator tamsulosin product in Australia, Flomaxtra. As noted previously, the former is a modified release formulation contained within a hard capsule while the latter is a film-coated prolonged release tablet. Therefore the sponsor submitted a justification for not providing such biopharmaceutic data.

Tamsulosin 400 mg daily was originally approved in the EU as a modified release, bead-filled capsule formulation under the tradename Omnic MR. The Marketing Authorisation Holder was Astellas Pharma Ltd. Many generic versions of tamsulosin 400 mg modified release capsules are now also registered and are currently marketed throughout Europe.

In about 2005, Astellas Pharma Ltd discontinued their modified-release, bead-filled capsule formulation (Omnic MR) and replaced it with a film-coated prolonged release tablet formulation. The sponsor for this submission (GlaxoSmithKline) claims that this new formulation incorporates an oral-controlled absorption system (OCAS) and has the tradename Omnic OCAS in many European countries but has the tradename Flomaxtra XL in the UK.

Tamsulosin 400 mg was first approved in Australia in 1999. The sponsor for this formulation (GSK) claims that, as in the EU, it was originally approved as a modified release, bead-filled capsule formulation, registered under the trade name Flomax and sponsored by CSL Limited. Again, as in the EU, the modified-release bead-filled capsule formulation has been replaced

²⁷ The tamsulosin which was used in the co-administration arm and in the tamsulosin monotherapy arm of CombAT was the modified-release, bead-filled capsule formulation (MR) which was the only tamsulosin formulation

in Australia (in about 2006) by a prolonged-release film-coated tablet formulation. Unlike the situation in the EU and elsewhere in the world, this prolonged release formulation is now the only tamsulosin product currently registered in Australia. The MR capsule formulation is now no longer available in Australia despite, as the sponsor notes, having been approved and widely used in patients between 1999 and 2006. The new prolonged release formulation has the tradename Flomaxtra and the sponsor is CSL Ltd. However, GSK has not provided any actual biopharmaceutic data in support of this.

Duodart was developed as a solid oral dosage form to be bioequivalent to Avodart and to Flomax/Omnice MR (modified release capsules) taken concomitantly. Bioequivalence of Duodart to Avodart and to Flomax was demonstrated in Study ARI109882. Study ARI10021 demonstrated bioequivalence between Flomax and Omnice MR, thereby linking Duodart to the positive outcome of Study ARI40005 (CombAT).

Pharmacokinetics & metabolism – Tamsulosin modified-release formulation

The first of two references supplied by the sponsor in support of the justification for not providing biopharmaceutic data was one by van Dijk et al, 2006.²⁸ This was a review article comparing the modified-release (MR) and the oral-controlled absorption system (OCAS) formulations of tamsulosin in BPH. The Delegate has summarised this article below.

An immediate-release formulation of tamsulosin would exhibit rapid absorption with a correspondingly rapid increase in plasma concentration upon oral administration. This would lead to the possibility of cardiovascular AEs such as hypotension and so a modified-release (MR) capsule was developed. The latter employs a multi-unit layer coated pellet technology. The pellets have a drug core and the modified-release characteristics are provided by the layer surrounding the pellets. These are hydrated in the gastrointestinal tract, where the drug is released.

As noted by van Dijk et al, the pharmacokinetics of tamsulosin MR have been assessed in several studies in both young and elderly subjects. Absorption of tamsulosin from the MR formulation after oral administration is gradual, with a bioavailability of about 100% under fasting conditions. The pharmacokinetics are dose linear following single and multiple doses. The time to maximum concentration, T_{max} , is 4-5 hours under fasting conditions and 6-7 hours when administered with food. Fasting conditions increase the bioavailability by 30% and the mean maximum plasma concentration, C_{max} by 40-70% compared with fed conditions. All clinical studies were based upon the recommendation that tamsulosin MR capsules should be taken after a meal, as also specified in the US labelling and the EU SmPC. A summary of the PK properties of tamsulosin MR is given in Table 18.

Table 18: PK properties of 400 mg of the MR and of the OCAS formulations of tamsulosin administered under fed conditions

	Tamsulosin MR	Tamsulosin OCAS
t_{max} (h)	6–7	8–9
C_{max} (ng/ml)	14	6
$t_{1/2}$ (h)	14–15	14–15
Clearance (l/h)	2.88	2.88
Volume of distribution (l/kg)	16	16
Plasma protein binding (%)	99	99

MR: Modified release; OCAS: Oral-controlled absorption system.

²⁸ van Dijk, MM et al, Tamsulosin – modified-release and oral-controlled absorption system formulations in the treatment of benign prostatic hyperplasia, Therapy 2006; 3: 237-246.

Pharmacokinetics & metabolism – Tamsulosin oral-controlled absorption system formulation

The review by van Dijk et al summarised a study which assessed the single-dose pharmacokinetics of three OCAS 400 mg formulations (each differing in the total amount of gel-enhancing agent) and tamsulosin MR 400 mg capsules in young healthy volunteers. The pharmacokinetics of all 3 OCAS formulations differed from the MR formulation in several ways. Firstly, C_{max} values were reduced, yielding smaller peak-to-trough ratios and more constant 24 hour plasma concentrations. Secondly, the total drug exposure as assessed by AUC was lower. Thirdly, the pharmacokinetics of tamsulosin OCAS were not affected by concomitant food intake. On the other hand, the OCAS formulation had only minor effects on T_{max} or on the terminal elimination half-life. Among the three tested OCAS formulations, one was selected for further development and its PK profile was confirmed in subsequent studies. A summary of the pharmacokinetic properties of tamsulosin OCAS is given in Table 18. The Delegate noted that Table 18 does not give any information about comparative values of AUC for either formulation. However, in the study just described by van Dijk, the AUC for the OCAS formulation was lower than that for the MR formulation. The Delegate requested that the sponsor provide details of the comparative AUC values of the two formulations in its pre-ACPM response.

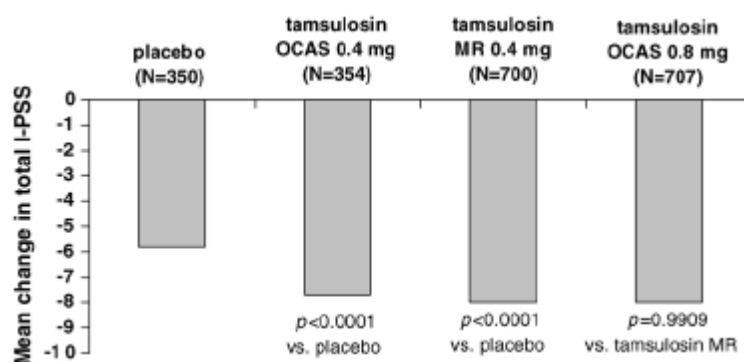
Comparative clinical efficacy of tamsulosin MR formulation and tamsulosin OCAS formulation

In a Phase IIIa randomized, double-blind trial, a total of 2152 patients received placebo, tamsulosin OCAS 400 mg, tamsulosin OCAS 800 mg or tamsulosin MR 400 mg for 12 weeks. This study by Chapple et al, 2005 was the second of the two references provided by the sponsor in the justification package.²⁹ Its findings were also summarised by the van Dijk article which was the first reference. Tamsulosin MR 400 mg was administered according to the prescribing information, that is, after breakfast.

In the Chapple et al study, after a 2-week single-blind, placebo run-in period, 2152 men of at least 45 years of age with lower urinary tract symptoms suggestive of BPH were randomised to placebo (n = 357), tamsulosin OCAS 400 mg (n = 361), tamsulosin MR 400 mg (n = 710) or tamsulosin OCAS 800 mg (n = 724). For the mean reduction in total I-PSS from baseline to endpoint, there was no statistically significant difference between tamsulosin OCAS 800 mg (8.0 points or 42.4%) and tamsulosin MR 400 mg (8.0 points or 43.2%, $p = 0.9909$). The reductions with both tamsulosin OCAS 400 mg (7.7 points or 41.7%) and tamsulosin MR 400 mg (8.0 points or 43.2%) were statistically significantly larger than with placebo (5.8 points or 32.0% with the respective differences being 1.7 and 2.0 points, $p < 0.0001$ for each comparison). The mean changes in total I-PSS from baseline to endpoint are shown in Figure 12.

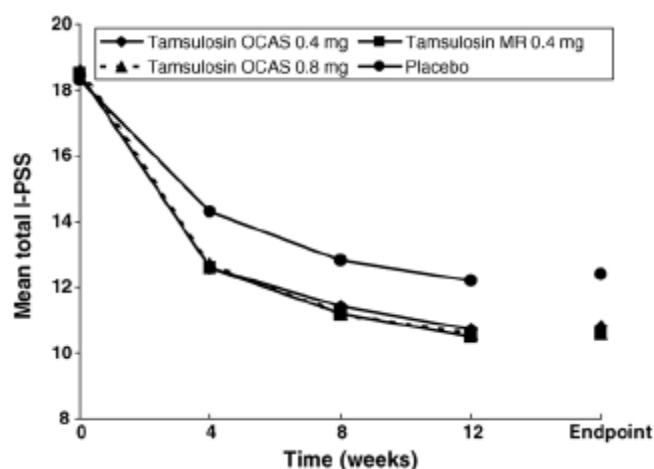
Figure 12: Mean change in total I-PSS from baseline to endpoint (ITT)

²⁹ Chapple CR et al, Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): Efficacy and Tolerability in a placebo and active comparator controlled Phase IIIa study. *European Urology Supplements* 2005; 4: 33-44.



The effect of the different treatments on the total I-PSS over time is displayed in Figure 13.

Figure 13: Effect of treatment on mean total I-PSS over time (ITT)



Thus the new OCAS formulation of tamsulosin at a dose of 400 mg and the old MR formulation of tamsulosin at a dose of 400 mg were similarly effective and superior to placebo in relieving lower urinary tract symptoms suggestive of BPH.

Comparative clinical safety of tamsulosin MR formulation and tamsulosin OCAS formulation

In the Phase IIIa study assessing 2152 patients, all treatments were well tolerated with dizziness and abnormal ejaculation the most frequently reported AEs. The incidence rates of various treatment-emergent AEs are displayed in Table 19.

Table 19: Treatment-emergent AEs reported by at least 2% of patients

N (%) of patients with:	Placebo N = 356	Tamsulosin OCAS 0.4 mg N = 360	Tamsulosin MR 0.4 mg N = 709	Tamsulosin OCAS 0.8 mg N = 722
At least one TEAE	71 (20%)	93 (26%)	168 (24%)	192 (27%)
At least one treatment-related AE	25 (7%)	40 (11%)	82 (12%)	103 (14%)
Most common TEAEs				
Dizziness	5 (1.4%)	5 (1.4%)	9 (1.3%)	17 (2.4%)
Retrograde ejaculation	1 (0.3%)	6 (1.7%)	10 (1.4%)	18 (2.5%)
TEAEs attributed to α_1 -AR blockade				
Non-cardiovascular	7 (2.0%)	16 (4.4%)	36 (5.1%)	57 (7.9%)
Cardiovascular	8 (2.2%)	9 (2.5%)	23 (3.2%)	28 (3.9%)
All ^a	13 (3.7%)	25 (6.9%)	55 (7.8%)	80 (11.1%)

^a Some AEs may occur simultaneously in one patient.

It should be noted that this study was not powered for detecting differences between active treatments in the incidence rates of AEs. The remaining question to be resolved in the context of this application is whether the tamsulosin OCAS 400 mg is better tolerated or more safe than the old tamsulosin MR formulation at the same dose of 400 mg. Table 19 indicates that there were no major differences in the incidence rates of dizziness or of retrograde ejaculation between these two formulations. There appears to be an error in the table above which is taken from the article. In several places in the text, the rate of dizziness for tamsulosin MR 400 mg was quoted as 1.7%, not 1.3%. So the rate of dizziness on the MR formulation was slightly greater than on the OCAS formulation. What are not shown in the table are the comparative incidence rates of all abnormal ejaculation related TEAEs, 1.9% for the OCAS and 3.1% for the MR. Non-cardiovascular TEAEs attributable to α_1 -AR blockade were all pooled (that is, all abnormal ejaculation related TEAEs, headache, asthenia, fatigue, somnolence, rhinitis, nasal dryness, nasal congestion and nasal obstruction). They occurred at a lesser rate in the OCAS group (4.4%) than in the MR group (5.1%). This difference

would appear to have been driven by the difference in the rates of abnormal ejaculation events. Furthermore, the rates of all non-abnormal ejaculation events in the non-cardiovascular pooling must have been slightly in favour of the MR formulation. Cardiovascular TEAEs attributable to α_1 -AR blockade were all pooled (that is, all dizziness-related TEAEs, palpitations, tachycardia, hypotension, orthostatic hypotension, dizziness postural, syncope, orthostatic/circulatory collapse and depressed level of/loss of consciousness). These events occurred at a lesser rate in the OCAS group (2.5%) than in the MR group (3.2%). Importantly, whereas none of the patients in the placebo or tamsulosin OCAS 400 mg groups reported any orthostatic hypotension, dizziness postural, syncope or orthostatic/circulatory collapse, there were 6 of these events in the tamsulosin MR 400 mg group (and 5 in the tamsulosin OCAS 800 mg group). A depressed level of or loss of consciousness was reported by 2 patients, one on tamsulosin OCAS 400 mg and one on tamsulosin MR 400 mg.

In the Phase IIIa study, during double-blind treatment, 3 patients died, 1 taking placebo, 1 taking tamsulosin MR 400 mg and 1 taking tamsulosin OCAS 800 mg. No death was considered treatment-related. As well, 31 patients (1.4%) experienced other serious TEAEs during double-blind treatment, 3 patients (0.8%) on placebo, 7 patients (1.9%) on tamsulosin OCAS 400 mg, 9 patients (1.3%) on tamsulosin MR 400 mg and 12 patients (1.7%) on tamsulosin OCAS 800 mg. These were considered treatment-related in none of the patients on placebo, 0.3% of patients receiving tamsulosin OCAS 400 mg (1 patient with swelling/dyspnoea exacerbated), 0.4% of patients receiving tamsulosin MR 400 mg (1 patient with loss of consciousness, 1 patient with paroxysmal arrhythmia and 1 patient with vertigo and orthostatic hypotension) and 0.6% of patients receiving tamsulosin OCAS 800 mg (1 patient with AF, 1 patient with cardiac failure and atrial fibrillation (AF), 1 patient with angina pectoris and 1 patient with myocardial infarction).

There were 59 patients (2.7%) who discontinued from the study due to TEAEs, 6 patients (1.7%) on placebo, 14 patients (3.9%) on tamsulosin OCAS 400 mg, 11 patients (1.6%) on tamsulosin MR 400 mg and 28 patients (3.9%) on tamsulosin OCAS 800 mg. The AEs leading to treatment discontinuation were judged to be treatment-related in 0.6% (placebo), 1.9% (tamsulosin OCAS 400 mg), 1.3% (tamsulosin MR 400 mg) and 2.4% (tamsulosin OCAS 800 mg) of patients. None of these treatment-related AEs resulting in discontinuation were reported as serious AEs with placebo, whereas this was the case for 1 patient (0.3%, swelling/dyspnoea exacerbated) in the tamsulosin OCAS 400 mg, 1 patient (0.1%, vertigo/orthostatic hypotension) in the tamsulosin MR 400 mg and 3 patients (0.4%, AF, cardiac failure/AF and angina pectoris) in the tamsulosin OCAS 800 mg group.

The mean changes in supine systolic (SBP) and diastolic blood pressure (DBP) from baseline to Week 12 of treatment are shown diagrammatically in Figure 14.

Figure 14: Mean change in supine SBP and DBP from baseline to week 12 of treatment

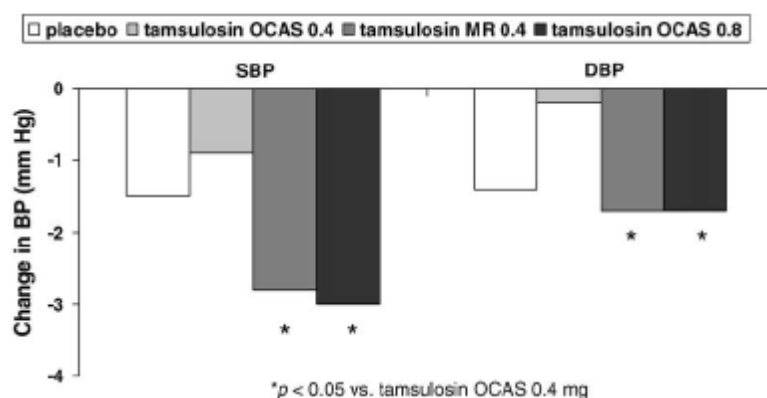


Table 20 shows the changes in vital signs measured in the standing position. It appears that there were decreases in SBP and DBP in all treatment groups, including the placebo group. There were greater reductions in supine SBP and DBP with both tamsulosin MR 400 mg and tamsulosin OCAS 800 mg when compared with tamsulosin OCAS 400 mg. Both sets of differences were statistically significant ($p < 0.05$).

Table 20: Effect of treatment on standing vital signs

Variable	Placebo N = 340	Tamsulosin OCAS 0.4 mg N = 344	Tamsulosin MR 0.4 mg N = 691 ^a	Tamsulosin OCAS 0.8 mg N = 690 ^b
Mean (S.D.) SBP: mmHg				
Baseline	139.1 (17.3)	139.3 (17.2)	138.5 (17.1)	138.9 (18.1)
Change at 12 weeks	-1.5 (14.0)	-2.2 (15.2)	-3.5 (15.5)	-3.5 (15.9)
Mean (S.D.) DBP: mmHg				
Baseline	83.7 (10.7)	82.9 (10.2)	83.5 (10.5)	83.3 (10.9)
Change at 12 weeks	-1.2 (9.5)	-0.5 (9.2)	-2.2 (9.8)	-2.1 (9.4)
Mean (S.D.) PR: bpm				
Baseline	73.2 (10.0)	73.1 (9.6)	72.9 (10.4)	73.0 (10.0)
Change at 12 weeks	-0.3 (9.6)	-0.8 (8.9)	-0.1 (10.4)	+0.2 (10.0)

Number of patients with data after 12 weeks of treatment.

^a N = 690 for PR.

^b N = 687 for PR.

The key difference between the safety profile of tamsulosin OCAS 400 mg and tamsulosin MR 400 mg would appear to be in the incidence rates of any orthostatic hypotension, dizziness postural, syncope or orthostatic/circulatory collapse.

In van Dijk et al, there is a summary of a double-blind, randomised, two-period crossover study in 40 healthy elderly males, comparing the cardiovascular safety of tamsulosin OCAS 400 mg and tamsulosin MR 400 mg. For the cardiovascular safety assessments, orthostatic stress tests were performed and vital signs were measured in the fasting state. An increase in the incidence of positive orthostatic stress tests was encountered in both tamsulosin OCAS 400 mg (17.5%) and tamsulosin MR 400 mg (31.7%) treated patients compared to pre-dose (2.5%). Tamsulosin OCAS caused significantly less orthostasis than tamsulosin MR based upon an analysis of discordant pairs (a positive test result for only one of the two treatments). The analysis of the vital signs confirmed that the OCAS formulation caused smaller BP reductions and increases in pulse rate compared to the MR formulation. This study demonstrated an improved cardiovascular tolerability of tamsulosin OCAS as compared to tamsulosin MR under fasting conditions. As noted by the authors, in interpreting these differences, it must be remembered that dosing of tamsulosin MR under fasting conditions is not recommended. They also point out that similar studies have demonstrated that lack of food intake decreases the cardiovascular tolerability of tamsulosin MR. They go on to point out that whether a similar difference exists between tamsulosin OCAS and tamsulosin MR

when both are taken after a meal has not been tested in clinical studies. However, it is known that the C_{max} is more than doubled for tamsulosin MR 400 mg compared with tamsulosin OCAS 400 mg in the fed state. The Delegate had already requested the sponsor to provide the comparative data for AUC.

Another important comment made by the investigators, Chapple et al, in relation to the Phase IIIa clinical study was that it was a study designed with registration in mind and because of this the patients enrolled may not have been fully representative of patients managed in real life clinical practice as those who were particularly prone to vasodilatory-related AEs such as patients with cardiovascular co-morbidity/medication were specifically excluded. The authors estimated that patients prone to such AEs may represent 30-40% of those presenting in everyday clinical practice who may require treatment for BPH symptomatology.

In the sponsor's justification for not submitting biopharmaceutic data, it summarises its arguments as follows: "...the main advantage of the OCAS tablet over the MR capsule is related to the lack of apparent effect on absorption in relation to food. In a Phase IIIa study the efficacy of tamsulosin OCAS 400 mg and tamsulosin MR 400 mg were demonstrated to be similar and the OCAS 400 mg formulation appeared to have only minor advantages with regard to tolerability". Based on the preceding full analysis of the safety data from the Phase IIIa study and other studies – an analysis which was more detailed than that provided in the sponsor's justification document – the Delegate disagreed with the sponsor's assertion that OCAS formulations have only minor advantages with regard to tolerability.

Risk Management Plan

The Delegate strongly endorsed all of the recommendations made in the RMP evaluation report, particularly those to do with breast and prostate cancer. The RMP as summarised does not appear to address the issue of patients switching from the innovator brand of tamsulosin (Flomaxtra) to the combination therapy, Duodart as it is essentially the EU document. There is a crucial need for this to be done. In the pre-ACPM response, the sponsor was requested to spell out in detail what steps it will undertake to mitigate the risks associated with this switching.

Risk-Benefit Analysis

Delegate Considerations

Data from the pivotal study, ARI40005, demonstrated that combination therapy with dutasteride 500µg once daily and tamsulosin 400 mg once daily, was significantly better at improving symptoms, compared with either monotherapy, as shown by the statistically significant reduction from baseline in IPSS at the 24-month endpoint. Consistent changes in all the secondary endpoints, for example, peak urinary flow rate and the proportions of subjects exhibiting changes in $IPSS \geq 2$, ≥ 3 and $\geq 25\%$ from baseline, were observed in favour of the combination therapy compared with either of the monotherapies. As noted by the clinical evaluator, there was not sufficient evidence presented by the sponsor for reduction of episodes of acute urinary retention or the reduction in the need for surgery related to BPH with the combination tablet (Duodart). These are quite specific clinical outcomes. Also neither of these was a primary efficacy endpoint and cannot be reflected therefore in the indication. The primary efficacy endpoint was improvement in symptoms as measured by change from baseline in IPSS. Other outcome measures such as change in prostate volume and change in peak urinary flow rate were secondary efficacy endpoints. The Delegate was strongly of the view that only the primary efficacy endpoint should be reflected in the wording of the indications. It is of interest to note that the approved indications in both the USA and the EU similarly reflect the primary endpoint only.

The evidence provided by the supportive studies, while not as robust as that provided by the pivotal studies, was internally consistent for each study and also consistent with the results of the pivotal study. The limitations of each of the supportive studies have already been pointed out by the clinical evaluator. ARI40002 was only a short-term, pilot study in a small group of 327 patients who were randomised. ARI40013, with 2385 subjects, did not achieve its planned sample size of 3000. The latter figure was chosen because it is the minimum number required to identify, with a probability of 90%, adverse events occurring with an incidence of at least 0.1%. There were no pre-defined hypotheses with respect to efficacy outcomes. Furthermore, the study was open-label and the two groups, those started on combination therapy and those on monotherapy, were not balanced with regard to baseline disease characteristics, deliberately so by the study design. Therefore it is not really possible to compare the efficacy outcomes between the two groups in ARI40013. All that can be concluded about the latter study is that the efficacy results moved in the same direction as those from the pivotal study.

As noted by the clinical evaluator, the safety profile of coadministration was favourable, with the nature and frequency of AEs reported in all three studies being consistent with the safety profiles of either monotherapy. Both dutasteride and tamsulosin are currently approved drugs for the treatment of BPH. No significant new safety concerns with coadministering the two drugs were identified. Some sexual (erectile dysfunction, loss of libido and disorders of ejaculation) and breast (nipple pain) adverse events were numerically higher in the combination drug group. However, these events were uncommon, not life-threatening and can be satisfactorily addressed in the product information. The Delegate noted that there has been some updating of the EU SmPC regarding the increased incidence of cardiac failure in subjects on the combination of dutasteride and tamsulosin but with the qualification that no causal relationship between Avodart (alone or in combination with an alpha-blocker) and cardiac failure has been established. There has, as yet, been no such updating of the US PI. There is currently under evaluation by the TGA a submission for an updating of the Australian-approved PI with regard to the issue of cardiac failure, similar to that in the EU SmPC.

By far the most important issue to arise in the consideration of this submission is that concerning the potential switching of large numbers of patients presently on the innovator formulation of tamsulosin, Flomaxtra 400 mg either as monotherapy or in combination as a separate medication with Avodart (dutasteride 500 µg) over to the combination therapy proposed for registration, Duodart. The Flomaxtra tamsulosin 400 mg medication is the prolonged-release tablet formulation whereas the tamsulosin component of Duodart is the MR formulation contained in a hard capsule. As noted earlier in this report, the key difference between prolonged release/OCAS and MR formulations of tamsulosin is in the incidence of AEs related to orthostatic hypotension/syncope/dizziness postural etc where the rate on the MR formulation is undeniably higher. This rate differential is exacerbated if the MR formulation is, for whatever reason, taken on an empty stomach. The Delegate shared the concern of both van Dijk et al and Chapple et al that a fraction of elderly males taking tamsulosin MR may not take their medication after a meal despite recommendations in the PI and CMI to the contrary. Therefore the same concern exists with regard to those patients who may not take their prescribed Duodart as directed and take it instead on an empty stomach. As noted by Chapple et al, it is important to realise that vasodilatory AEs such as orthostatic hypotension and syncope are not only unpleasant for the patient but can also lead to serious morbidity such as falls and fractures and even mortality.

Compared with the submission for an extension of indications for the monotherapy Avodart in combination with tamsulosin (PM-2009-02236-3-3), the risk-benefit balance for this

Duodart submission is not as clear cut.¹⁷ The one issue which has altered the risk-benefit balance is the issue discussed under the preceding point, that to do with patients switching from Flomaxtra 400 mg, either as monotherapy or as a separate tablet in combination with Avodart over to the combination proposed for registration, Duodart. On balance, the Delegate does not view this as a reason for rejection. In its own right, Duodart has been shown to be a safe and effective medication in the treatment of symptoms of BPH. Furthermore, the product has been approved in both the USA and the EU for an indication very similar to that proposed by the Delegate. However, the issue of possible switching will have to be addressed very seriously by the sponsor not only in the PI but also in the RMP and in the CMI. Patients and their prescribing doctors should be warned, unequivocally and clearly, that there is a potential risk of increased vasodilatory AEs such as orthostatic hypotension and syncope. One possible option would be to recommend a black box warning at the head of the PI warning of the potential; another would be the inclusion in the PI of a statement not permitting any switching. However, black box warnings are usually reserved for extremely serious safety issues. Any recommendation against switching would not, in all likelihood, be a practical alternative, especially if such a statement was not to be accompanied by precautionary statements about switching. The Delegate asked for advice from the ACPM in relation to these options. The sponsor was also invited to comment.

Another issue on which the Delegate sought the advice of the ACPM was his view that Duodart should really be reserved for second-line treatment. Even though in the pivotal study, CombAT, the subjects were randomised from the beginning into three treatment groups, one on the combination and each of the other two on a monotherapy, rational clinical practice is to test a monotherapy initially. The reasons for this are that there will be a certain percentage of patients whose symptoms will be adequately controlled on monotherapy and that testing therapies one at a time allows practitioners to attribute degrees of effectiveness and also adverse events to the responsible medication. Furthermore, both monotherapies are registered, approved treatments for the symptoms of BPH. As it stands, there is no clear advice in the Duodart PI as to where it is positioned in the treatment paradigm in relation to the monotherapies and this is a deficiency. For example there is no clear advice about the degree of seriousness of a patient's symptoms which would favour treatment with the fixed-dose combination over either of the monotherapies and what is more, this has not been prospectively tested. All that has been demonstrated is that, after two years of treatment, the combination has been shown to be more effective than either of the monotherapies. The question as to the exact time at which one should intervene in monotherapy treatment with combination treatment has not really been addressed. The Delegate was of the view that a patient should be given an adequate trial of a monotherapy before being exposed to the fixed-dose combination. The Delegate asked for the specific advice of the ACPM regarding this issue. The sponsor was also invited to comment.

Overall, the Delegate was satisfied that, with appropriate precautionary statements in the PI and in the CMI and also with appropriate and committed strategies in the RMP, the risk-benefit balance is sufficient to recommend approval of the fixed-dose combination, Duodart for the following indication:

Treatment of moderate to severe symptoms of benign prostatic hyperplasia.

Sponsor's pre-ACPM Response

The sponsor expressed its willingness to accept the revised Indication wording as proposed by the Delegate. The Delegate raised concerns regarding switching from the existing tamsulosin product to Duodart and has suggested that a black box warning or a statement preventing switching be included into the Duodart product information (PI). The sponsor

believed that Duodart is a safe and efficacious product and did not agree to the inclusion of these statements in the PI. Similarly, the sponsor believed that Duodart provides an important addition to the current treatment options for BPH and it did not believe that it should be restricted to second line therapy.

As there is no direct bioequivalence data between Duodart and Flomaxtra, the focus of the sponsor's discussion, and also that of the Delegate, is on the differences between Flomax and Flomaxtra. The Delegate discussed a publication by Chapple et al, 2005. In this study, two strengths of tamsulosin OCAS (400 mg and 800 mg) was compared with tamsulosin MR 400 mg and placebo. No concerns were raised with regard to the comparative efficacy of the tamsulosin OCAS 400 mg and tamsulosin MR 400 mg formulations and so its discussion focussed on safety and tolerability.

Overall, the authors of the study state that all treatments were well tolerated. The number of patients with at least one treatment emergent adverse event (TEAE) was 26% versus 24% in the OCAS 400 mg and MR 400 mg groups respectively. The number of patients with at least one treatment-related AE was 11% in the OCAS 400 mg group and 12% in the MR 400 mg group. The most common TEAEs were dizziness and retrograde ejaculation. As noted by the Delegate there is some discrepancy in the incidence rate for dizziness. Without having further data, it is not possible to determine which of these two values is correct and so the sponsor disagreed with the Delegate's statement that the "rate of dizziness on the MR formulation was slightly greater than on the OCAS formulation." However, regardless of the correct value, the paper clearly states that statistical analysis of all dizziness related terms combined showed no statistically significant difference between tamsulosin OCAS 400 mg and tamsulosin MR 400 mg.

The paper also stated that none of the patients in the placebo or tamsulosin OCAS 400 mg groups reported orthostatic hypotension, dizziness postural, syncope or orthostatic/circulatory collapse where as there were 6 of these events in the tamsulosin MR 400 mg group and 5 of these events in the tamsulosin OCAS 800 mg group. The sponsor believed that the way these results have been reported in the paper, that is, reported as raw numbers, is inherently biased given the difference in patient numbers in each group (the tamsulosin OCAS 400 mg had approximately half the number of patients as the tamsulosin MR 400 mg group). The overall percentage of subjects in the tamsulosin MR group with a reported event of orthostatic hypotension, dizziness postural, syncope or orthostatic/circulatory collapse was low: 0.8% (6/709). From further discussion in the paper it appears that only one of these six events was considered serious.

The Delegate also discussed the results for change in blood pressure from baseline for the each study groups. The paper includes a graphical representation of the change in supine SBP and DBP from baseline to 12 weeks of treatment (Figure 14). First impressions of this graph, suggest that the tamsulosin MR 400 mg and the tamsulosin OCAS 800 mg formulations result in a much greater drop in supine SBP and DBP as compared to the tamsulosin OCAS 400 mg formulation. Whilst these differences were shown to be statistically significant, the actual numerical difference between the OCAS 400 mg and MR 400 mg groups was less than 2 mmHg for both SBP and DBP. These differences are unlikely to represent any real clinical significance. Furthermore, the change from baseline for the tamsulosin OCAS 400 mg group was less than that reported for placebo. If the tamsulosin MR 400 mg formulation is compared to placebo, the difference between the two groups is <1.5 mmHg for SBP and <1 mmHg DBP, a difference that is unlikely to have any clinical significance.

With regard to the effect of treatment on standing vital signs, results for the tamsulosin MR 400 mg formulation showed a slightly greater reduction in mean SBP and DBP at 12 weeks as

compared to the tamsulosin OCAS 400 mg formulation. Again the actual differences between the two treatment groups for both SBP and DBP was <2 mmHg. With regard to pulse rate at 12 weeks, the tamsulosin OCAS 400 mg group showed a greater decrease from baseline than the tamsulosin MR 400 mg group (-0.8 bpm versus -0.1 bpm respectively). None of these differences are likely to have any clinical significance.

The Delegate has stated that “the Delegate would disagree with the sponsor’s assertion that OCAS formulations have only minor advantages with regard to tolerability.” Given the overall number of TEAEs reported in the Chapple study, the lack of statistical difference in all dizziness related terms, the small differences reported in both supine and standing blood pressure, the small differences in TEAEs attributed to α 1-AR blockade and patient discontinuation rates, the sponsor disagreed with the Delegate and stood by its original statement that “...the main advantage of the OCAS tablet over the MR capsule is related to the lack of apparent effect on absorption in relation to food. In a Phase IIIa study the efficacy of tamsulosin OCAS 400 mg and tamsulosin MR 400 mg were demonstrated to be similar and the OCAS 400 mg formulation appeared to have only minor advantages with regard to tolerability.”

The safety results from the pivotal study provided in our submission (CombAT, study number ARI40005) must not be overlooked. This large, double-blind controlled study in 4844 patients compared the combination of tamsulosin 400 mg and dutasteride 500µg with tamsulosin 400 mg or dutasteride 500µg alone (n= 1610, 1623 and 1611 respectively). Both the clinical evaluator and the Delegate have noted that the safety profile of the co-administration was favourable, with the nature and frequency of AEs reported being consistent with the safety profiles of either monotherapy. In relation to some of the adverse events discussed above, the incidence rates in the combination therapy group for dizziness postural, syncope, hypotension and orthostatic hypotension were all below 1%. The overall incidence rate for dizziness was 3%.

The Delegate has stated in his risk/benefit discussion that “the key difference between prolonged release/OCAS and MR formulations of tamsulosin is in the incidence of AEs related to orthostatic hypotension/syncope/dizziness postural etc. where the rate on the MR formulation is undeniably higher.”

Whilst the Chapple study did show a difference in the rate of these events with the MR formulation, the overall rates were still low (<1%). Similarly, the CombAT study, a much larger study which monitored patients for a much longer duration, also showed that these events were uncommon with an incidence rate of less than 1%.

The Delegate also refers to a study by van Dijk et al (2006) which contains a summary of a study comparing tamsulosin OCAS 400 mg and tamsulosin MR 400 mg under fasting conditions. The sponsor did not dispute that there are differences between these two formulations when taken under fasted conditions and as such the labelling for Duodart has always stated that it must be taken approximately 30 minutes after the same meal each day. This point has been further emphasised in the revised version of the PI submitted with this response. As noted by the Delegate, the van Dijk paper also points out that whether a similar difference exists between tamsulosin OCAS and tamsulosin MR when taken after a meal has not been tested in clinical studies.

The sponsor also addressed the other issues raised by the Delegate.

1. The sponsor was to confirm that the study ARI40001 has been formally evaluated by the TGA. This was done.

2. Comparative data for AUC between tamsulosin OCAS formulations and tamsulosin MR formulations when administered to subjects in the fed state.

The sponsor replied that the following table has been taken from a publication by Michel et al (2005) and compares the AUC of the tamsulosin OCAS and tamsulosin MR formulations in the fed state.³⁰ This table was included in the Absorption subsection of the Pharmacokinetics section of the revised PI included with this response.

	Tamsulosin MR 400 mg (n=12) Mean (range)	Tamsulosin OCAS 400 mg (n=12) Mean (range)
AUC _∞ (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)

Whilst the AUC values for the MR formulation are higher than those for the OCAS formulation, both formulations show a very high degree of interpatient variability. These values should not be looked at in isolation but need to be looked at in conjunction with the clinical results seen in the CombAT study and the study reported by Chapple. Despite what may appear as a large difference in AUC, there does not appear to be a corresponding large difference in adverse event rates.

3. The sponsor was to provide detailed revisions to its RMP for Australia to incorporate strategies to minimise the risk of adverse effects, particularly those related to vasodilatory effects of tamsulosin, in patients switching from Flomaxtra either as monotherapy or in combination with Avodart over to the fixed-dose combination Duodart.

The sponsor replied that orthostasis signs and symptoms have already been identified as a risk with tamsulosin-containing products and monitoring of these events is currently included in the RMP. The RMP evaluator has agreed that routine pharmacovigilance monitoring of these events is acceptable. With regard to additional strategies to minimise the risk of adverse effects in patients switching from Flomaxtra to Duodart, the sponsor have revised both the PI and the CMI to include additional statements about the importance of taking Duodart after food and the possible consequences if taken on an empty stomach. The sponsor has also included additional information in the PI regarding the pharmacokinetic differences between Flomaxtra and the tamsulosin component of Duodart. Finally, as part of the sponsor's promotional and educational materials, it will provide information explaining the differences between the two tamsulosin formulations and emphasise the importance of taking Duodart after food.

4. The various options canvassed by the Delegate for managing the issue of switching in the PI, including a black box warning and/or the inclusion of a statement not permitting switching.

The sponsor replied that it did not agree to the inclusion of a black box warning or the inclusion of a statement not permitting switching from the current Australian tamsulosin product (Flomaxtra) to Duodart. The Delegate himself has stated that "black box warnings are usually reserved for extremely serious safety situations and any recommendation against

³⁰ Michel MC et al. The pharmacokinetic profile of tamsulosin oral controlled system (OCAS). European Urology Supplements 2005; 4: 15 – 24.

switching would not, in all likelihood, be a practical alternative.” The sponsor did not believe that switching between Flomaxtra and Duodart would result in an extremely serious safety situation and therefore does not warrant a black box warning. As discussed above the sponsor believed that when Duodart is taken as directed, there are only minor differences in the tolerability of the two tamsulosin formulations.

The CombAT study has shown that co-administration of dutasteride and tamsulosin is safe and well tolerated with events such as dizziness postural, syncope, hypotension and orthostatic hypertension being reported at rates below 1%. Similarly, the rate of these events for the tamsulosin MR 0.4mg group in the Chapple study was also < 1%. The small differences in blood pressure changes observed in the Chapple study are unlikely to be of clinical significance and although the authors conclude that the tamsulosin OCAS formulation showed a tendency towards a better tolerability ratio than tamsulosin MR 400 mg, the percentages of subjects who withdrew due to a treatment emergent adverse event was higher in the OCAS 400 mg group than the MR group. These results do not support the level of warning suggested by the Delegate.

A statement not permitting switching between Flomaxtra and Duodart is impractical, is not in the best interests of patients and is unlikely to be followed by healthcare professionals. The sponsor did not believe that the tendency towards a difference as seen in the Chapple study was reason enough to warrant either a black box warning or a statement not permitting switching between Flomaxtra and Duodart. Duodart has been approved in the EU for an indication very similar to that proposed by the Delegate. As both the OCAS and MR tamsulosin formulations are available in Europe, there will also be situations where patients may be switched from the tamsulosin OCAS formulation to Duodart. However, this issue of switching was not raised as a major concern by the Reference Member State (Germany) and no further warning or advisory statements were required in the product labelling.

However, in order to address the concerns of the Delegate, the sponsor has included additional statements in the revised PI enclosed with this response that explain the pharmacokinetic differences between the current Australian tamsulosin product and Duodart, the minor differences in adverse event rates as reported in the Chapple study and the importance of taking Duodart after a meal. The sponsor has also agreed to provide similar information in its promotional and educational materials as part of its risk management activities.

5. The issue of Duodart as second-line treatment compared to each of the monotherapies.

The sponsor noted that dutasteride and tamsulosin have different yet complimentary mechanisms of action. These complementary effects provide a sound rationale for 5ARI/alpha blocker combination therapy, which provides greater and more durable benefits than either monotherapy.

Sequential treatments are often used in areas where tolerance to the first treatment agent develops and so a second agent is required in order to adequately control symptoms again. This would be a typical scenario in the management of hypertension for example. In the treatment of BPH, an alpha blocker will provide symptomatic relief but it will not reduce the progression of the disease. Therefore, when a patient's symptoms are no longer adequately controlled by the alpha-blocker, the disease may have progressed to the point where surgical treatment would be required. Noting however that this patient population is predominantly elderly and so surgery may not be an option. Delaying the start of treatment with dutasteride could lead to an increased risk of disease progression or delaying the start of treatment with an alpha-blocker could lead to a delay in symptom relief.

As was seen in the CombAT trial, patients may present initially with a higher risk of progression. These patients would particularly benefit from combination therapy as a first line treatment in order to provide rapid symptom relief as well as reducing the risk of disease progression. Approximately half of the patients in the CombAT study were treatment naïve. The degree of improvement achieved with combination therapy was similar in both treatment naïve and previously treated patients.

Additionally, the superiority of combination over monotherapies is acknowledged in current International treatment guidelines for BPH guidelines. The European Association of Urology guidelines (Madersbacher, 2004) state: “The combination therapy of 5ARI’s and alpha-blockers seems to be more beneficial and durable than by monotherapy with either one of these drugs.”³¹ Similarly the Canadian guidelines (Nickel, 2010) state: “The combination of an alpha-adrenergic receptor blocker and a 5-alpha reductase inhibitor is an appropriate and effective treatment strategy for patients with LUTS associated with prostatic enlargement.”³¹ Clinical trial results have shown that combination therapy results in significant improvement in symptoms score and peak urinary flow compared with either of the mono-therapy options. Combination medical therapy can effectively delay symptomatic disease progression, while combination therapy and/or 5 alpha reductase mono-therapy is associated with decreased risk of urinary retention and/or prostate surgery. (Level 1, Grade A Recommendation).” Finally, from a local perspective, the Australian Medicines Handbook states: The combination of an 5ARI with a selective alpha-blocker is more effective than either alone in delaying clinical progression of BPH and that combination treatment should be considered for men who are at high risk of progression.

Similar to any other treatment consideration, the most suitable treatment option, be it monotherapy or combination therapy, can only be determined after careful consideration of an individual patients disease state and needs. The use of combination therapy should not be restricted to second line treatment.

Advisory Committee Consideration

The Delegate asked for the advice of the ACPM on the following issues:

- Given the Delegate’s concerns about the situation of patients switching to Duodart from either Flomaxtra monotherapy or from the combination of Flomaxtra and Avodart, does the ACPM agree that the risk-benefit balance permits approval with appropriate warnings in the PI and CMI together with appropriate RMP strategies?
- Does the ACPM agree that the heightened risk of vasodilatory-related AEs on tamsulosin MR formulations compared with tamsulosin prolonged release formulations such as OCAS warrants considerable strengthening of the relevant warnings and precautions in the PI? What are the ACPM’s views on possible options such as a black box warning or a statement in the PI not permitting switching?
- Does the ACPM agree that the section on Dosage and Administration should have a statement that Duodart must never be taken in the fasting state?
- Does the ACPM agree that Duodart should not be recommended to be used as first-line treatment in the management of BPH? Should this be reflected in the indications?

³¹ Nickel, J. et al. 2010 update: Guidelines for the management of benign prostatic hyperplasia. Collaborative Consensus Document prepared for the Canadian Urological Association by the Canadian Prostate Health Council and the CUA Guidelines Committee.

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the approval of Duodart for the indication:

For the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH).

In making this recommendation, the ACPM considered the matter of first line and second line therapy and reinforced its expectation that prescribers will exercise ongoing due caution with appropriate dose titration when prescribing fixed dose combinations.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) which should be made prior to approval include:

- caution against administration on an empty stomach in the Dosage and administration section
- warnings about the heightened risk of vasodilatory related adverse events, such as hypotension, in the Precautions section
- strict protocols for switching between the currently approved dutasteride 500 µg and tamsulosin 400 µg monotherapies, and the proposed fixed-dose combination.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Duodart 500µg /400µg hard capsules containing dutasteride / tamsulosin hydrochloride 500 µg / 400 µg for the indication:

DUODART is indicated for the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH).

As a condition of registration, the full implementation of the Risk Management Plan version 02 dated 31 August 2008, as agreed with the Office of Product Review, must be completed.

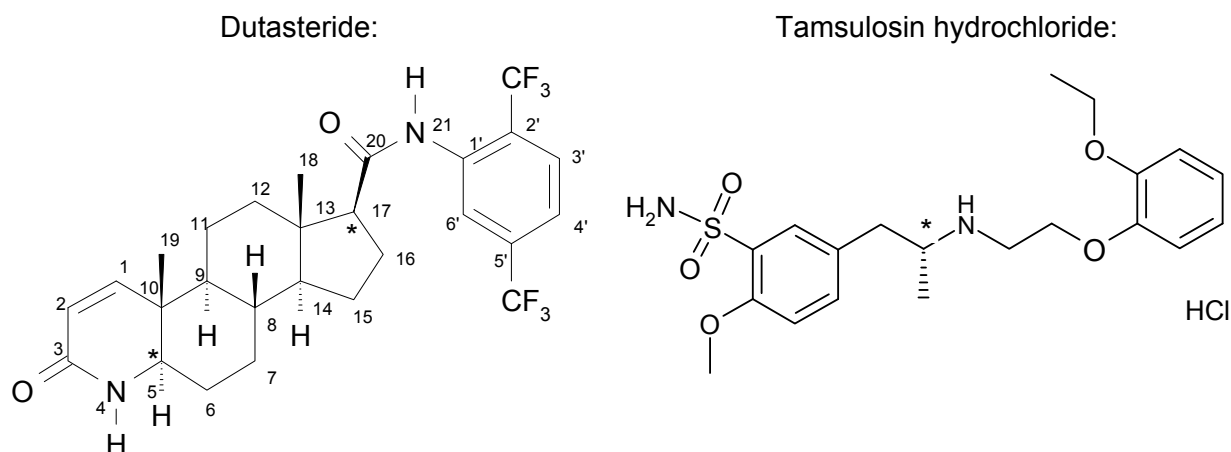
Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

DUODART® 500µg/400µg
PRODUCT INFORMATION

NAME OF THE MEDICINE Dutasteride/tamsulosin hydrochloride

Structure:



Dutasteride:

Chemical Name: 4-Azaandrost-1-ene-17-carboxamide, *N*-(2,5-Bis(trifluoromethyl)phenyl)-3-oxo-, (5 α , 17 β)-

Molecular Formula: C₂₇H₃₀F₆N₂O₂

CAS Number: 164656-23-9

Tamsulosin hydrochloride:

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

Molecular Formula: C₂₀H₂₈N₂O₅S · HCl

CAS Number: 106463-17-6

DESCRIPTION

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 isopropanol.

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.

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)

PHARMACOLOGY

Pharmacodynamics:

Mechanism of Action

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

Dutasteride inhibits both type 1 and type 2, 5 α -reductase isoenzymes, which are responsible for the conversion of testosterone to 5 α -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 have not been studied; however, the effects of the combination would not be expected to be different from those of dutasteride and tamsulosin administered separately.

Dutasteride

Dutasteride lowers DHT levels, reduces prostate volume, improves lower urinary tract symptoms and urine flow and reduces the risk of 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 μ g, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 500 μ g 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 5 α -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 HCl component in DUODART 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 DUODART (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.

Pharmacokinetics:

Bioequivalence was demonstrated between DUODART 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 DUODART 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 500µg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours. Absolute bioavailability in man is approximately 60% relative to a 2 hour i.v. 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 DUODART and the current Australian tamsulosin formulation. The following table has been taken from published literature:

	Tamsulosin MR 0.4 mg* (n=12) Mean (range)	Tamsulosin OCAS 0.4mg** (n=12) Mean (range)
AUC _{0-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 DUODART (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 DUODART 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 500µg 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, CYP2C9, CYP2C19, 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 5 α -reductase. The activity of 6 β -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 metabolized 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. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Elimination

Dutasteride

Dutasteride is extensively metabolized. Following oral dosing of dutasteride 500 μ g/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 μ g/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 DUODART, 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 500µg 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 ($30 \leq CL_{cr} < 70 \text{ mL/min/1.73m}^2$) or moderate-severe ($10 \leq CL_{cr} < 30 \text{ mL/min/1.73m}^2$) renal impairment and 6 normal subjects ($CL_{cr} > 90 \text{ mL/min/1.73m}^2$). 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 ($CL_{cr} < 10 \text{ mL/min/1.73m}^2$) have not been studied.

Hepatic impairment

Dutasteride

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, 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

Duodart is contraindicated for use in children.

CLINICAL TRIALS

Dutasteride co-administered with tamsulosin

The following statements reflect the information available on dutasteride and tamsulosin when administered together as separate medications. No clinical studies have been conducted with the fixed-dose combination capsule, DUODART (see Pharmacodynamics).

Dutasteride 500µg/day (n=1,623), tamsulosin 400µg/day (n=1,611) or the combination of dutasteride 500µg plus tamsulosin 400µg (n=1,610) [total number of patients = 4844] were evaluated in men with moderate to severe symptoms of BPH who had prostate volumes ≥30mL and a PSA values within the range 1.5 – 10 ng/mL in a multicenter, multinational, randomized double-blind, parallel group study. Approximately 52% of subjects had previous exposure to 5α-reductase inhibitor or alpha-blocker treatment. Efficacy endpoints during the first 2 years of treatment were change in International Prostate Symptoms Score (IPSS), maximum urine flow rate (Qmax) and prostate volume. IPSS is an 8-item instrument based on AUA-SI with an additional question on quality of life. This study was designed as a 4 year study with a pre-defined analysis at 2 years.

Results following 2 years of treatment are presented below:

Parameter	Time-point	Combination	Dutasteride	Tamsulosin
IPSS (units)	[Baseline] Month 24 (change from baseline)	[16.6] -6.2	[16.4] -4.9 ^a	[16.4] -4.3 ^b
Qmax (mL/sec)	[Baseline] Month 24 (change from baseline)	[10.9] 2.4	[10.6] 1.9 ^{c*}	[10.7] 0.9 ^{d*}
Prostate Volume	[Baseline] (mL) Month 24 (% change from baseline)	[54.7] -26.9	[54.6] -28.0	[55.8] 0.0*
Prostate Transition Zone Volume	[Baseline] (mL) Month 24 (% change from baseline)	[27.7] -23.4	[30.3] -22.8	[30.5] 8.8*
BPH Impact Index (BII) (units)	[Baseline] Month 24 (change from baseline)	[5.3] -2.1	[5.3] -1.7*	[5.3] -1.5*
IPSS Question 8 (BPH-related Health Status)	[Baseline] Month 24 (change from baseline)	[3.6] -1.4	[3.6] -1.1*	[3.6] -1.1*

- ^a Combination achieved significance ($p < 0.001$) vs. dutasteride from Month 3
^b Combination achieved significance ($p < 0.001$) vs. tamsulosin from Month 9
^c Combination achieved significance ($p \leq 0.006$) vs. dutasteride from Month 6
^d Combination achieved significance ($p < 0.001$) vs tamsulosin from Month 6
^{*} $p < 0.01$

Dutasteride monotherapy

The efficacy and safety of dutasteride 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 30ccs) and a Prostate Specific Antigen (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 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 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 1: Rates of occurrence and risk reduction of urological events

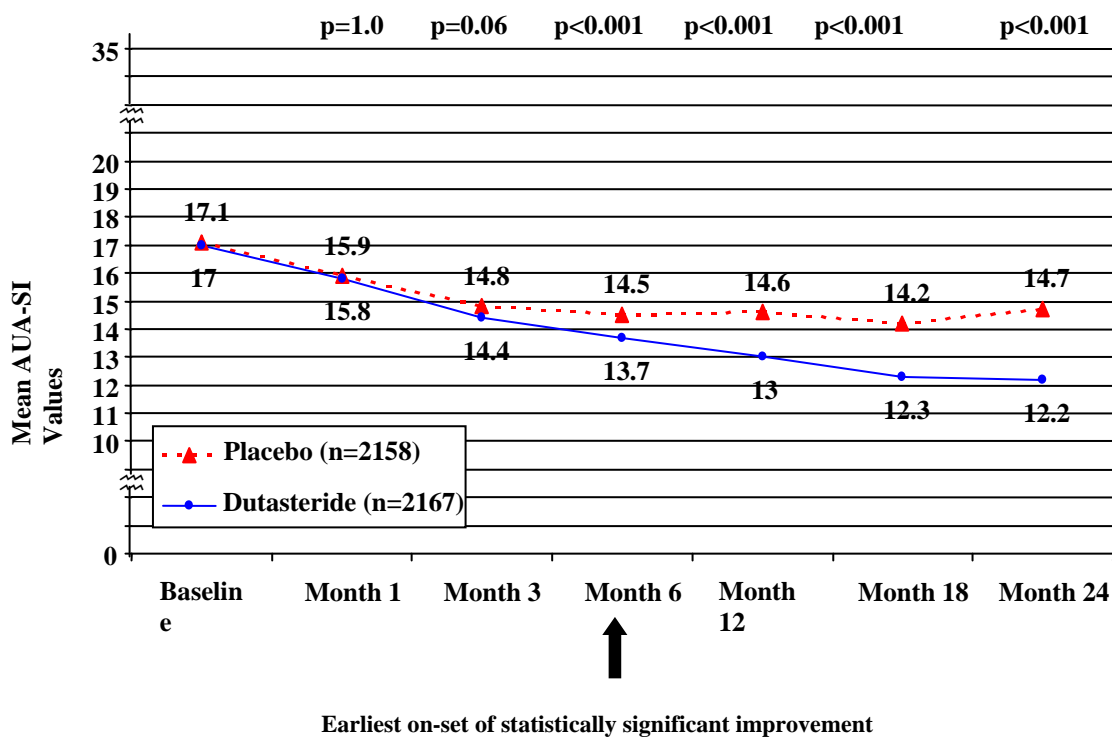
Event	Placebo (n = 2158)	Avodart (n = 2167)	Risk Reduction
Acute urinary retention (AUR)	4.2% (n=90)	1.8% (n=39)	57% ($p < 0.001$)
BPH-related surgical intervention	4.1% (n=89)	2.2% (n=47)	48% ($p < 0.001$)

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 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.

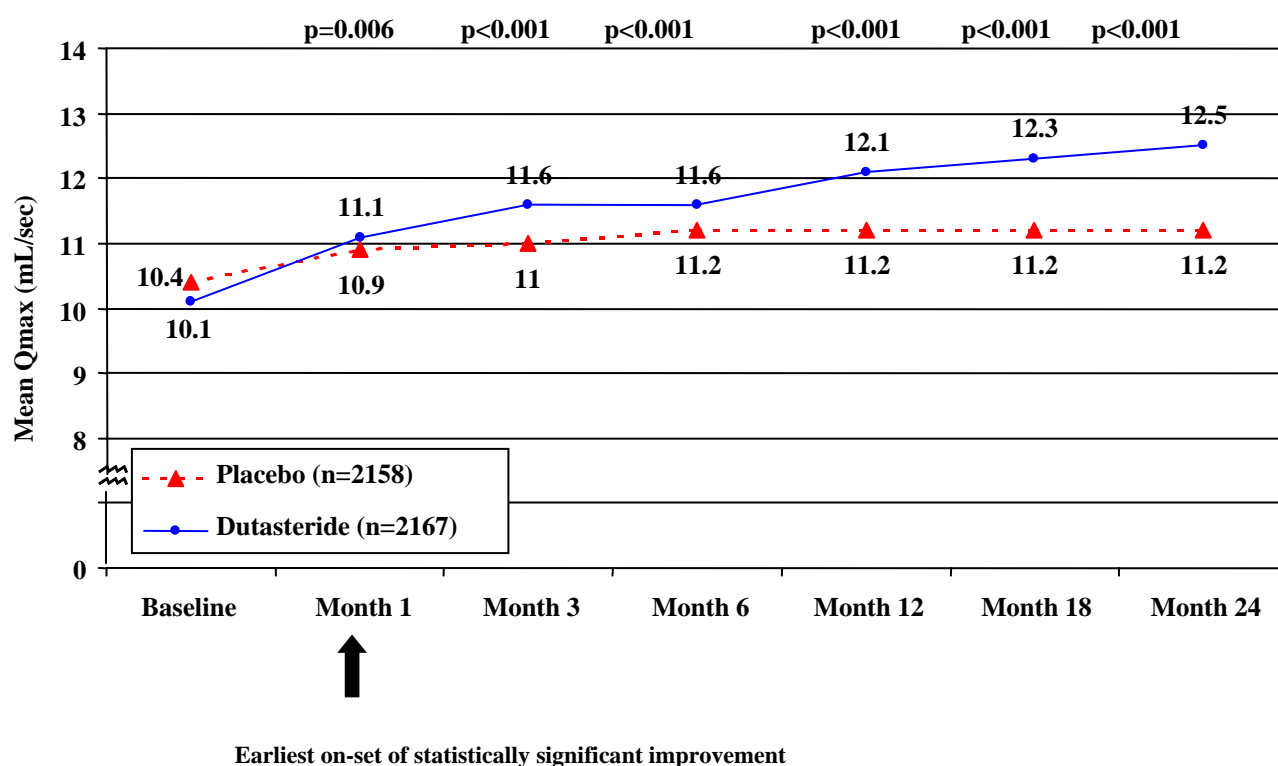
Figure 1: Pooled AUA-SI Mean Values (At Visit)



Maximum Urinary Flow (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 \geq 15 mL/sec) in both treatment groups across the three studies. Statistically significant improvement in Qmax 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.

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



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 54.9cc at baseline to 42.1cc) at Month 12 compared with a mean reduction of 0.5% (from 54.0cc to 53.7cc) in the placebo group. At 24 months, dutasteride decreased prostate volume by 25.7% (from 54.9cc at baseline to 41.2cc) 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 µg/day for 24 months) was similar to that of placebo (see **ADVERSE REACTIONS**).

Breast neoplasia:

In dutasteride BPH monotherapy clinical trials, providing 3374 patient years of exposure to dutasteride, there were 2 cases of 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. The relationship between long-term use of dutasteride and male breast cancer is unknown.

Tamsulosin monotherapy

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.

INDICATIONS

DUODART is indicated for the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH).

CONTRAINDICATIONS

DUODART is contraindicated in:

- patients with known hypersensitivity to dutasteride, other 5 α -reductase inhibitors, tamsulosin hydrochloride or any component of the preparation.
- women and children (see 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.

PRECAUTIONS

DUODART should be prescribed after careful benefit risk assessment and after consideration of alternative treatment options including monotherapies.

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 Pregnancy and Lactation).

DUODART must be taken approximately 30 minutes after the same meal each day (see Dosage and Administration). Taking DUODART on an empty stomach may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

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 DUODART and periodically thereafter.

PSA concentration is an important component of the screening process to detect prostate cancer. Generally, a serum PSA concentration greater than 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy. Physicians should be aware that a baseline PSA less than 4 ng/mL in patients taking DUODART does not exclude a diagnosis of prostate cancer.

Dutasteride causes a decrease in serum PSA levels by approximately 50% after 6 months in patients with BPH, even in the presence of prostate cancer. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL). Therefore to interpret an isolated PSA value in a man treated with DUODART for 6 months or longer,

PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.

Any sustained increases in PSA levels while on DUODART should be carefully evaluated, including consideration of non-compliance to therapy with DUODART.

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 DUODART therapy, no adjustment to its value is necessary.

Orthostatic Hypotension

As with other α -1 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 DUODART 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 DUODART.

Patients beginning treatment with DUODART 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 DUODART (see Pharmacokinetics) and the potential for orthostatic hypotension (particularly if DUODART is taken on an empty stomach). Patients should be advised to take DUODART 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.

Blood Donation

Men being treated with any dutasteride-containing products, including DUODART, 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 α -1 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 lead to increased procedural complications during the 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 DUODART 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.

Renal Impairment

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

Hepatic Impairment

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

DUODART is contraindicated in patients with severe hepatic impairment.

Effects on Fertility

There have been no studies to investigate the effect of DUODART 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 5 α -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 μ g /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 or impairment of ejaculation. Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Use in Pregnancy (Category X):

DUODART is contraindicated for use in women.

Dutasteride

As with other 5-alpha 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 5-alpha 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:

DUODART is contraindicated for use in women.

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

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.

Genotoxicity:

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

Interactions with other medicines:

There have been no drug interaction studies for DUODART. 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 5- α 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 metabolized by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6.

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

Tamsulosin: Strong and Moderate Inhibitor of CYP3A4 or CYP2D6: Tamsulosin is extensively metabolized, mainly by CYP3A4 or CYP 2D6.

Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A4) has resulted in increases in the C_{max} and AUC of tamsulosin. 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 increases in the C_{max} and AUC of tamsulosin. 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.

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

Cimetidine:

Concomitant administration of tamsulosin hydrochloride (400 µg) 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 DUODART and other drugs containing α-1 adrenergic blockers is therefore contraindicated (see Contraindications).

PDE-5 Inhibitors

Caution is advised when alpha-adrenergic antagonists, including tamsulosin-containing products such as DUODART, are coadministered with PDE-5 inhibitors. Alpha-adrenergic antagonists and PDE-5 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 µg for seven days followed by 800 µg 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 DUODART.

Digoxin and Theophylline

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

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

Concomitant administration of tamsulosin hydrochloride (400 µg/day for two days, followed by 800µg/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 µg /day) and a single i.v. dose of furosemide (20 mg) produced an 11% to 12% reduction in the C_{max} 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.

Cholestyramine

Dutasteride: Administration of a single 5-mg dose of dutasteride followed 1 hour later by a 12 g dose of cholestyramine does not affect the relative bioavailability of dutasteride.

Other products

Dutasteride: *In vitro* studies demonstrate that dutasteride does not displace 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, nonsteroidal 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.

Ability to Drive and Use Machines:

There have been no studies to investigate the effect of DUODART 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 DUODART.

ADVERSE EFFECTS

There have been no clinical trials conducted with DUODART; 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 µg and tamsulosin 400 µg 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

Year 2 data from the CombAT study have shown that the incidence of any investigator-judged drug-related adverse event during the first and second years of treatment respectively was 22% and 5% for dutasteride + tamsulosin co-administration therapy, 14% and 5% for dutasteride monotherapy and 13% and 4% for tamsulosin monotherapy. The higher incidence of adverse events in the co-administration therapy group in the first year of treatment was due to a higher incidence of reproductive disorders, specifically ejaculation disorders, observed in this group.

The following investigator-judged drug-related adverse events (with an incidence of greater than or equal to 1%) have been reported during Years 1 and 2 of the CombAT study.

Adverse event	Incidence during year 1 of treatment			Incidence during year 2 of treatment		
	Dutasteride + Tamsulosin (n=1610)	Dutasteride (n=1623)	Tamsulosin (n=1611)	Dutasteride + Tamsulosin (n=1424)	Dutasteride (n=1457)	Tamsulosin (n=1468)
Impotence	7%	5%	3%	1%	1%	<1%
Altered (decreased) libido	5 %	4%	3%	<1%	<1%	<1%
Ejaculation disorders	9%	2%	3%	<1%	<1%	<1%
Breast disorders†	2%	2%	<1%	<1%	1%	<1%
Dizziness	1%	<1%	1%	<1%	<1%	<1%

†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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) 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.

Skin and subcutaneous tissue disorders:

Rare: Alopecia (primarily body hair loss), hypertrichosis.

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.

GSK does not hold the safety database for any single ingredient tamsulosin product; therefore the adverse reactions and frequency categories below 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 ($\geq 1/100$ <1/10)	Uncommon ($\geq 1/1000$ <1/100)	Rare ($\geq 1/10,000$ <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		Syncope	
Reproductive system and breast disorders		Abnormal ejaculation		Priapism
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Immune system disorders		Rash Pruritis Urticaria	Angioedema	
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 Warnings and Precautions). Infrequent reports of skin desquamation have also been received.

DOSAGE AND ADMINISTRATION

DUODART must be taken approximately 30 minutes after the same meal each day. Patients should be advised that DUODART 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 DUODART combination therapy, please read the information under Pharmacodynamic effects.

Populations

- **Adult males (including elderly)**

The recommended dose of DUODART is one capsule (500 µg dutasteride /400 µg tamsulosin) taken orally approximately 30 minutes after the same meal each day (see Pharmacokinetics – 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 DUODART pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see Pharmacokinetics – Renal impairment).

- **Hepatic impairment**

The effect of hepatic impairment on DUODART pharmacokinetics has not been studied (see Warnings and Precautions and Pharmacokinetics – Hepatic impairment). DUODART is contraindicated in patients with severe hepatic impairment.

OVERDOSAGE

No data are available with regard to overdosage of DUODART. 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 µg.

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

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

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.

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C.

DUODART capsules (dutasteride 500µg/tamsulosin hydrochloride 400µg): oblong, hard-shell capsules with a brown body and an orange cap imprinted with GS 7CZ in black ink [each containing one oblong, opaque, dull-yellow dutasteride soft gelatin capsule (500µg dutasteride) and white to off-white tamsulosin hydrochloride pellets (400µg tamsulosin hydrochloride)].

DUODART capsules are packed into the following container closure systems:
Opaque, white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners:

7 capsules in 40 mL bottle

30 capsules in 100 mL bottle

90* capsules in 200 mL bottle

* This pack size not currently marketed.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4
436 Johnston Street
Abbotsford Victoria 3067
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of TGA Approval: 20 October 2010

DUODART® is a registered trade mark of the GlaxoSmithKline group of companies.

Version No. 1

Therapeutic Goods Administration

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