Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dutasteride/Tamsulosin Rowa 0.5 mg/0.4 mg hard capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride (equivalent to 0.367 mg tamsulosin).

Excipient(s) with known effect:
Each capsule contains traces of lecithin (may contain soya oil).
Each capsule contains 299.46 mg propylene glycol, which is equivalent to 4.27 mg/kg.
Each capsule contains 0.026 mg sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Dutasteride/Tamsulosin Rowa are oblong hard gelatin capsules of approximately 24.2 mm x 7.7 mm with brown body and beige cap printed with C001 in black ink.

Each hard capsule contains one dutasteride soft gelatin capsule and tamsulosin hydrochloride modified release pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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.
For information on effects of treatment and patient populations studied in clinical trials please see section 5.1.

4.2 Posology and method of administration

Posology

Adults(includingelderly):
The recommended dose of Dutasteride/Tamsulosin Rowa is one capsule (0.5 mg/ 0.4 mg) daily.

Where appropriate Dutasteride/Tamsulosin Rowa may be used to substitute dual therapy (dutasteride and tamsulosin hydrochloride) to simplify treatment regimen.
Under prescriber criteria, change from dutasteride or tamsulosin hydrochloride monotherapy to Dutasteride/Tamsulosin Rowa could be considered.

Renalimpairment
The effect of renal impairment on dutasteride-tamsulosin pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment (see section 4.4 and 5.2).

Hepaticimpairment
The effect of hepatic impairment on dutasteride-tamsulosin pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment (see section 4.4 and section 5.2). In patients with severe hepatic impairment, the use of Dutasteride/Tamsulosin Rowa is contraindicated (see section 4.3).

Method of administration

For oral use.

Patients should be advised to take the capsules approximately 30 minutes after the same meal each day. 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.

4.3 Contraindications

Dutasteride/Tamsulosin Rowa is contraindicated in:
-women and children and adolescents (see section 4.6)
-patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin (including tamsulosin-induced angio-edema), soya, peanut or any of the other excipients listed in section 6.1
-patients with a history of orthostatic hypotension
-patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Combination therapy should be prescribed after careful benefit risk assessment due to the potential increased risk of adverse events (including cardiac failure) and after consideration of alternative treatment options including monotherapies.

Cardiac failure
In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤1%) and variable between the studies (see section 5.1).

Effects on prostate specific antigen (PSA) and prostate cancer detection
Before therapy with Dutasteride/Tamsulosin Rowa is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. Dutasteride/Tamsulosin Rowa causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment.

Patients receiving Dutasteride/Tamsulosin Rowa should have a new PSA baseline established after 6 months of treatment with Dutasteride/Tamsulosin Rowa. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on Dutasteride/Tamsulosin Rowa may signal the presence of prostate cancer (particularly high grade cancer) or noncompliance to therapy with Dutasteride/Tamsulosin Rowa and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor (see section 5.1). In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with Dutasteride/Tamsulosin Rowa does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established (see section 5.1).

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/Tamsulosin Rowa. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing Dutasteride/Tamsulosin Rowa therapy, no adjustment to its value appears necessary.

Prostate cancer and high grade tumours
Results of one clinical study (the REDUCE study) in men at increased risk of prostate cancer revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men compared to placebo. The relationship between dutasteride and high grade prostate cancer is not clear. Men taking Dutasteride/Tamsulosin Rowa should be regularly evaluated for prostate cancer risk including PSA testing (see section 5.1).

Renal impairment
The treatment of severely renal impaired patients (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied.

Hypotension
As with other α 1-adrenoceptors antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared.

Vigilance for hypotension is important in patients who are treated with selective α adrenoceptors antagonists like tamsulosin concomitant with phosphodiesterase 5 inhibitor (PDE5 inhibitors such as sildenafil), because both class effect can potentially cause hypotension (see section 4.5).

Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may lead to increased procedural complications during the operation.

The initiation of therapy with Dutasteride/Tamsulosin Rowa in patients for whom cataract surgery is scheduled is therefore not recommended. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with Dutasteride/Tamsulosin Rowa in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

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

Leaking capsules
Dutasteride is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking capsules (see section 4.6). If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

Inhibitors of CYP3A4 andCYP2D6
Concurrent administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 and CYP2D6 can increase tamsulosin exposure (see section 4.5).

Hepatic impairment
Dutasteride/Tamsulosin Rowa has not been studied in patients with liver disease. Caution should be used in the administration of Dutasteride/Tamsulosin Rowa to patients with mild to moderate hepatic impairment (see section 4.2, section 4.3 and section 5.2).

Breast neoplasia
Breast cancer has been reported in men taking dutasteride in clinical trials (see section 5.1) and during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies for Dutasteride/Tamsulosin Rowa have been performed. The following information is available on the individual components.

Dutasteride
For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection, please see section 4.4.

Effects of other drugs on the pharmacokinetics of dutasteride
Use together with CYP3A4 and/or P-glycoprotein-inhibitors:
Dutasteride is mainly eliminated via metabolism. In vitro studies indicate that this metabolism is catalyzed by CYP3A4 and CYP3A5. No formal interaction studies have been performed with potent CYP3A4 inhibitors. However, in a population pharmacokinetic study, dutasteride serum concentrations were on average 1.6 to 1.8 times greater, respectively, in a small

number of patients treated concurrently with verapamil or diltiazem (moderate inhibitors of CYP3A4 and inhibitors of P -glycoprotein) than in other patients.

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-alpha 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.

Administration of 12 g cholestyramine one hour after a 5 mg single dose of dutasteride did not affect the pharmacokinetics of dutasteride.

Effects of dutasteride on the pharmacokinetics of other drugs
In a small study (N=24) of two weeks duration in healthy men, dutasteride (0.5 mg daily) had no effect on the pharmacokinetics of tamsulosin or terazosin. There was also no indication of a pharmacodynamics interaction in this study.

Dutasteride has no effect on the pharmacokinetics of warfarin or digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P -glycoprotein. In vitro interaction studies indicate that dutasteride does not inhibit the enzymes CYP1A2, CYP2D6, CYP2C9, CYP2C19 or CYP3A4.

Tamsulosin
Caution in concomitant administration with tamsulosin and other hypotensive effects drugs (e.g anesthetic agents, PDE5 inhibitors and other α1 adrenoceptors antagonists). Dutasteride-tamsulosin should not be used in combination with other α1 adrenoceptors antagonists.

Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin hydrochloride. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and Cmax of tamsulosin hydrochloride by a factor of 2.8 and 2.2, respectively.

Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a Cmax and AUC of tamsulosin that had increased by a factor of 1.3 and 1.6, respectively, but these increases are not considered clinically relevant.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril or theophylline. Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, whereas furosemide a fall, but as levels remain within the normal range posology need not be adjusted.

In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinon, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide and chlormadinon.

Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

4.6 Fertility, pregnancy and lactation

Dutasteride/Tamsulosin Rowa is contraindicated for use by women. There have not been conducted studies to evaluate the effect of Dutasteride/Tamsulosin Rowa on pregnancy, lactation and fertility. The following information is available from studies with the individual components (see section 5.3).

Pregnancy
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 fetus, inhibit the development of the external genitalia of the fetus (see section 4.4). Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride. It is not known whether a

male fetus 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).

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.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits showed no evidence of fetal harm.

For information on preclinical data, see section 5.3.

Breast-feeding
It is not known whether dutasteride is excreted in human milk

Fertility
Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men (see section 5.1). The possibility of reduced male fertility cannot be excluded.

Influences of tamsulosin hydrochloride on sperm counts or sperm function have not been investigated.

4.7 Effects on ability to drive and use machines

Dutasteride/Tamsulosin Rowa could have minor influence on the ability to drive and use machines. However, patients should be aware of the fact that symptoms such as dizziness can occur using tamsulosin.

4.8 Undesirable effects

Dutasteride in combination with the alpha-blocker tamsulosin

Data from the 4 year CombAT Study, comparing dutasteride 0.5 mg (n=1623) and tamsulosin 0.4 mg (n=1611) once daily alone and in combination (n=1610) have shown that the incidence of any investigator-judged drug-related adverse event during the first, second, third and fourth years of treatment respectively was 22%, 6%, 4% and 2% for dutasteride/tamsulosin combination therapy, 15%, 6%, 3% and 2% for dutasteride monotherapy and 13%, 5%, 2% and 2% for tamsulosin monotherapy. The higher incidence of adverse events in the combination 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 have been reported with an incidence of greater than or equal to 1% during the first year of treatment in the CombAT Study; the incidence of these events during the four years of treatment is shown in the following table.

System Organ Class	**Adverse Reaction**	**Incidence during treatment period**			
		Year 1	Year 2	Year 3	Year 4
	Combination[a] (n)	(n=1610)	(n=1428)	(n=1283)	(n=1200)
	Dutasteride	(n=1623)	(n=1464)	(n=1325)	(n=1200)
	Tamsulosin	(n=1611)	(n=1468)	(n=1281)	(n=1112)
Nervous system disorders	Dizziness				
	Combination[a]	1.4%	0.1%	<0.1%	0.20%
	Dutasteride	0.7%	0.1%	<0.1%	<0.1%
	Tamsulosin	1.3%	0.4%	<0.1%	0%
Cardiac disorders	Cardiac failure (composite term[b])				
	Combination[a]	0.2%	0.4%	0.2%	0.2%
	Dutasteride	<0.1%	0.1%	<0.1%	0%
	Tamsulosin	0.1%	<0.1%	0.4%	0.2%
Reproductive system and breast disorders	Impotence[c]				

	Combination[a]	6.3%	1.8%	0.9%	0.4%
	Dutasteride	5.1%	1.6%	0.6%	0.3%
	Tamsulosin	3.3%	1.0%	0.6%	1.1%
	Altered (decreased) libido[c]				
	Combination[a]	5.3%	0.8%	0.2%	0%
	Dutasteride	3.8%	1.0%	0.2%	0%
	Tamsulosin	2.5%	0.7%	0.2%	<0.1%
	Ejaculation disorders[c]				
	Combination[a]	9.0%	1.0%	0.5%	<0.1%
	Dutasteride	1.5%	0.5%	0.2%	0.3%
	Tamsulosin	2.7%	0.5%	0.2%	0.3%
	Breast disorders[d]				
	Combination[a]	2.1%	0.8%	0.9%	0.6%
	Dutasteride	1.7%	1.2%	0.5%	0.7%
	Tamsulosin	0.8%	0.4%	0.2%	0%

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

b Cardiac failure composite term comprised of cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.

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

d Includes breast tenderness and breast enlargement. In addition the undesirable effects of individual component is based on information available in the public domain. The frequencies of adverse events may increase when the combination therapy is used.

In addition, the undesirable effects of component separately are based on information available in the public domain. The frequency of adverse effects may increase when the combination therapy is used.

The frequency of adverse reactions identified from clinical trials:
Common; ≥1/100 to <1/10, Uncommon; ≥1/1000 to <1/100, Rare; ≥1/10,000 to <1/1000, Very rare; <1/10,000. Within each SOC grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Adverse reactions**	**Dutasteride[a]**	**Tamsulosin[b]**
Nervous system disorders	Syncope	-	Rare
	Dizziness	-	Common
	Headache		Uncommon
Cardiac disorders	Cardiac failure (Composite term[1])	Uncommon[c]	
	Palpitations		Uncommon
Vascular disorders	Orthostatic hypotension		Uncommon
Respiratory, thoracic and mediastinal disorders	Rhinitis		Uncommon
Gastrointestinal disorders	Constipation		Uncommon
	Diarrhoea		Uncommon
	Nausea		Uncommon
	Vomiting		Uncommon
Skin and subcutaneous disorders	Angioedema		Rare
	Stevens-Johnson syndrome		Very Rare
	Urticaria		Uncommon
	Rash		Uncommon
	Pruritis		Uncommon
Reproductive system and breast disorders	Priapism		Very Rare
	Impotence[3]	Common	-
	Altered (decreased) libido[3]	Common	-
	Ejaculation disorders[34]	Common	Common

	Breast disorders[2]	Common	
General disorders and administration site disorders	Asthenia		Uncommon

[a] Dutasteride: from BPH monotherapy clinical studies.
[b] Tamsulosin: from EU Core Safety Profile for tamsulosin.
[c] REDUCE study (see section 5.1).

1 Cardiac failure composite term comprised of cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.
2 Includes breast tenderness and breast enlargement.
3 These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is not known.
4 Includes semen volume decreased.

Other data
The REDUCE study revealed a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo (see sections 4.4 and 5.1). Whether the effect of dutasteride to reduce prostate volume, or study related factors, had an impact on the results of this study has not been established.

The following has been reported in clinical trials and post-marketing use: male breast cancer (see section 4.4).

Post marketing Data
Adverse events from world-wide post-marketing experience are identified from spontaneous post-marketing reports; therefore the true incidence is not known.

Dutasteride:
Immune system disorders
Not known: Allergic reactions, including rash, pruritus, urticaria, localized edema, and angioedema.

Psychiatric disorders
Not known: Depression.

Skin and subcutaneous tissue disorders
Uncommon: Alopecia (primarily body hair loss), hypertrichosis.

Reproductive system and breast disorders
Not known: Testicular pain and testicular swelling.

Tamsulosin:

Post-marketing experience: In addition to the adverse events listed above, atrial fibrillation arrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use. Because these spontaneously reported events are from the worldwide post marketing experience, the frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

During cataract surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of tamsulosin during post-marketing surveillance (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

No data are available with regards to over dosage of Dutasteride/Tamsulosin Rowa. The following statements reflect the information available on the individual components.

Dutasteride
In volunteer studies, single daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg. There is no specific antidote for dutasteride, therefore, in suspected over dosage symptomatic and supportive treatment should be given as appropriate.

Tamsulosin
Symptoms
Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

Treatment
In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help then volume expanders and, when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins. Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52

Dutasteride-tamsulosin is a combination of two drugs: dutasteride, a dual 5 α-reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of α1a and α1d adrenoreceptors. Both mechanisms of action are complementary to improve symptoms, urinary flow and reduce the risk of acute urinary retention (AUR) and the need for BPH related surgery.

Dutasteride reduces circulating levels of dihydrotestosterone (DHT) by inhibiting both type 1 and type 2, 5a-reductase isoenzymes which are responsible for the conversion of testosterone to DHT.
Tamsulosin binds selectively and competitively to the postsynaptic α 1-adrenoceptors, in particular to subtypes α 1A and α 1D. It brings about relaxation of prostatic and urethral smooth muscle.

Dutasteride in combination with tamsulosin
No non-clinical neither clinical studies in patients have been conducted with Dutasteride/Tamsulosin Rowa.

The following information is available on dutasteride and tamsulosin co-administration therapy.
Clinical studies reviewing the combined therapy with the 5α-reductase inhibitor dutasteride and the α1-adrenergic antagonist tamsulosin, have shown significant improvements from baseline compared with either drug alone.

Dutasteride 0.5 mg/day (n = 1,623), tamsulosin 0.4 mg/day (n = 1,611) or the co-administration of Dutasteride 0.5 mg plus tamsulosin 0.4 mg (n = 1,610) were evaluated in male subjects with moderate to severe symptoms of BPH who had prostates ≥30ml and a PSA value within the range 1.5 - 10 ng/mL in a 4 year multicenter, multinational, randomized double-blind, parallel group study. Approximately 53% of subjects had previous exposure to 5-alpha reductase inhibitor or alpha-blocker treatment. The primary efficacy endpoint during the first 2 years of treatment was change in International Prostate Symptom Score (IPSS), an 8-item instrument based on AUA-SI with an additional question on quality of life. Secondary efficacy endpoints at 2 years included maximum urine flow rate (Qmax) and prostate volume. The combination achieved significance for IPSS from Month 3 compared to dutasteride and from Month 9 compared to tamsulosin. For Qmax combination achieved significance from Month 6 compared to both dutasteride and tamsulosin.

The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH -related surgery. After 4 years of treatment, combination therapy statistically significantly reduced the risk of AUR or BPH - related surgery (65.8% reduction in risk p<0.001 [95% CI 54.7% to 74.1%]) compared to tamsulosin monotherapy. The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 11.9% for tamsulosin (p<0.001). Compared to dutasteride monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6% (p=0.18 [95% CI -10.9% to 41.7%]). The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 5.2% for dutasteride.

Secondary efficacy endpoints after 4 years of treatment included time to clinical progression (defined as a composite of: IPSS deterioration by ≥4 points, BPH-related events of AUR, incontinence, urinary tract infection (UTI), and renal insufficiency) change in International Prostate Symptom Score (IPSS), maximum urine flow rate (Qmax) and prostate volume. IPSS is an 8-item instrument based on the AUA-SI with an additional question on quality of life. Results following 4 years of treatment are presented below:

Parameter	Time-point	Combination	Dutasteride	Tamsulosin
AUR or BPH related surgery (%)	Incidence at Month 48	4.2	5.2	11.9a
Clinical progression* (%)	Month 48	12.6	17.8b	21.5a
IPSS (units)	[Baseline] Month 48 (Change from Baseline)	[16.6] -6.3	[16.4] -5.3b	[16.4] -3.8a
Qmax (mL/sec)	[Baseline] Month 48 (Change from Baseline)	[10.9] 2.4	[10.6] 2.0	[10.7] 0.7a
Prostate Volume (ml)	[Baseline] Month 48 (% Change from Baseline)	[54.7] -27.3	[54.6] -28.0	[55.8] +4.6a
Prostate Transition Zone Volume (ml)#	[Baseline] Month 48 (% Change from Baseline)	[27.7] -17.9	[30.3] -26.5	[30.5] 18.2a
BPH Impact Index (BII) (units)	[Baseline] Month 48 (Change from Baseline)	[5.3] -2.2	[5.3] -1.8b	[5.3] -1.2a
IPSS Question 8 (BPH-related Health Status) (units)	[Baseline] Month 48 (Change from Baseline)	[3.6] -1.5	[3.6] -1.3b	[3.6] -1.1a

Baseline values are mean values and changes from baseline are adjusted mean changes.
* Clinical progression was defined as a composite of: IPSS deterioration by ≥4 points, BPH-related events of AUR, incontinence, UTI, and renal insufficiency.
# Measured at selected sites (13% of randomized patients)
a. Combination achieved significance (p<0.001) vs. tamsulosin at Month 48 b. Combination achieved significance (p<0.001) vs. dutasteride at Month 48.

Clinical efficacy and safety of dutasteride

Dutasteride 0.5 mg/day or placebo was evaluated in 4,325 male subjects with moderate to severe symptoms of BPH who had prostates ≥30ml and a PSA value within the range 1.5 - 10 ng/mL in three primary efficacy 2-year multicenter, multinational, placebo controlled, double-blind studies. The studies then continued with an open-label extension to 4 years with all patients remaining in the study receiving dutasteride at the same 0.5 mg dose. 37% of initially placebo-randomized patients and 40% of dutasteride-randomized patients remained in the study at 4 years. The majority (71%) of the 2,340 subjects in the open-label extensions completed the 2 additional years of open-label treatment.

The most important clinical efficacy parameters were American Urological Association Symptom Index (AUA-SI), maximum urinary flow (Qmax) and the incidence of acute urinary retention and BPH -related surgery.

AUA-SI is a seven-item questionnaire about BPH-related symptoms with a maximum score of 35. At baseline the average score was approximately 17. After six months, one and two years treatment the placebo group had an average improvement of 2.5, 2.5 and 2.3 points respectively, while the Avodart group improved 3.2, 3.8 and 4.5 points respectively. The differences between the groups were statistically significant. The improvement in AUA-SI seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies.

Qmax (maximum urine flow):

Mean baseline Qmax for the studies was approx. 10 ml/sec (normal Qmax = 15 ml/sec). After one and two years treatment the flow in the placebo group had improved by 0.8 and 0.9 ml/sec respectively and 1.7 and 2.0 ml/sec respectively in the Avodart group. The difference between the groups was statistically significant from Month 1 to Month 24. The increase in maximum

urine flow rate seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies.

Acute Urinary Retention and Surgical Intervention
After two years of treatment, the incidence of AUR was 4.2% in the placebo group versus 1.8% in the Avodart group (57% risk reduction). This difference is statistically significant and means that 42 patients (95% CI: 30-73) need to be treated for two years to avoid one case of AUR.
The incidence of BPH-related surgery after two years was 4.1% in the placebo group and 2.2% in the Avodart group (48% risk reduction). This difference is statistically significant and means that 51 patients (95% CI: 33-109) need to be treated for two years to avoid one surgical intervention.

Hair distribution
The effect of dutasteride on hair distribution was not formally studied during the phase III programme, however, 5 alpha-reductase inhibitors could reduce hair loss and may induce hair growth in subjects with male pattern hair loss (male androgenetic alopecia).

Thyroid function:
Thyroid function was evaluated in a one year study in healthy men. Free thyroxine levels were stable on dutasteride treatment but TSH levels were mildly increased (by 0.4 MCIU/mL) compared to placebo at the end of one year treatment. However, as TSH levels were variable, median TSH ranges (1.4 - 1.9 MCIU/mL) remained within normal limits (0.5 - 5/6 MCIU/mL), free thyroxine levels were stable within the normal range and similar for both placebo and dutasteride treatment, the changes in TSH were not considered clinically significant. In all the clinical studies, there has been no evidence that dutasteride adversely affects thyroid function.

Breast neoplasia:
In the 2 year clinical trials, providing 3,374 patient years of exposure to dutasteride, and at the time of registration in the 2 year open label extension, there were 2 cases of breast cancer reported in dutasteride - treated patients and 1 case in a patient who received placebo. In the 4 year CombAT and REDUCE clinical trials providing 17,489 patient years exposure to dutasteride and 5,027 patient years exposure to dutasteride and tamsulosin combination there were no cases of breast cancer reported in any treatment groups.
Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and longterm use of dutasteride.

Effects on male fertility
The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in healthy 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 parameters at all time points remained within the normal ranges and did not meet the 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 possibility of reduced male fertility cannot be excluded.

Cardiac failure:
In a 4 year BPH study of dutasteride in combination with tamsulosin in 4,844 men (the CombAT study) the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: dutasteride, (4/1,623, 0.2%) and tamsulosin, (10/1,611, 0.6%).

In a separate 4-year study in 8,231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL in the case of men 50 to 60 years of age, or 3 ng/mL and 10.0 ng/mL in the case of men older than 60 years of age) (the REDUCE study), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride 0.5 mg once daily (30/4105, 0.7%) compared to subjects taking placebo (16/4126, 0.4%). A post-hoc analysis of this study showed a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects taking dutasteride and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), or placebo and no alpha blocker (15/2727, 0.6%).

Prostate cancer and high grade tumours
In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL in the case of men 50 to 60 years of age, or 3 ng/mL and 10.0 ng/mL in the case of men older than 60 years of age) (the REDUCE study), 6,706 subjects had prostate needle biopsy (primarily protocol mandated) data available for analysis to determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6, 70%).

There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%) (p=0.15). In Years 1-2, the number of subjects with Gleason 8- 10 cancers was similar in the dutasteride group (n=17, 0.5%) and the placebo group (n=18, 0.5%). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the dutasteride group (n=12, 0.5%) compared with the placebo group (n=1, <0.1%) (p=0.0035). There are no data available on the effect of dutasteride beyond 4 years in men at risk of prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the dutasteride group (0.5% in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5%, respectively) (see section 4.4). There was no difference in the incidence of Gleason 7-10 cancers (p=0.81).

In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were (n=8, 0.5%) for dutasteride, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy.
The relationship between dutasteride and high grade prostate cancer is not clear.

Clinical efficacy and safety of tamsulosin
Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in the prostate and urethra, thereby improving voiding symptoms. It also improves the storage symptoms in which bladder instability plays an important role. These effects on storage and voiding symptoms are maintained during long-term therapy. The need for surgery or catheterization is significantly delayed.

A1-adrenoreceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

5.2 Pharmacokinetic properties

Comparative bioavailability between Dutasteride/Tamsulosin Rowa and concomitant dosing with dutasteride and tamsulosin capsules separately, was demonstrated through three different studies carried out in healthy volunteers.

The single dose comparative bioavailability study was performed under both the fast and fed conditions. A <50% reduction in Cmax was observed for the tamsulosin component of dutasteride -tamsulosin in the fed state compared to the fasted state. Food had minor (<10%) effect on AUC of tamsulosin.

Multiple dose comparative bioavailability study demonstrated that Dutasteride/Tamsulosin Rowa exhibited an equivalent rate and extent of absorption to the reference products in healthy subjects at steady state, under fed conditions.

Absorption
Dutasteride
Following oral administration of a single 0.5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60%. The bioavailability of dutasteride is not affected by food.

Tamsulosin
Tamsulosin is absorbed from the intestine and is almost completely bioavailable. Both the rate and extent of absorption of tamsulosin are reduced when taken within 30 minutes of a meal. Uniformity of absorption can be promoted by the patient always taking Dutasteride/Tamsulosin Rowa after the same meal. Tamsulosin shows dose proportional plasma exposure.
After a single dose of tamsulosin in the fed state, plasma concentrations of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, the mean steady state Cmax in patients is about two thirds higher than that reached after a single dose. Although this was observed in elderly patients, the same finding would also be expected in younger patients.

Distribution

Dutasteride

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (>99.5%). Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months.

Steady state serum concentrations (Css) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Tamsulosin

In man tamsulosin is about 99% bound to plasma proteins. The volume of distribution is small (about 0.21/kg).

Metabolism

Dutasteride

Dutasteride is extensively metabolized *in vivo*. *In vitro*, dutasteride is metabolized by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite.

Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged 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.

Tamsulosin

Tamsulosin has a low first pass effect, being metabolized slowly. Most tamsulosin is present in plasma in the form of unchanged active substance. It is metabolised in the liver. In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin. In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin hydrochloride metabolism by other CYP isozymes. Inhibition of CYP3A4 and CYP2D6 drug metabolising enzymes may lead to increased exposure to tamsulosin hydrochloride (see section 4.4 and 4.5). None of the metabolites are more active than the original compound.

Elimination

Dutasteride

Dutasteride is extensively metabolised in vivo. In vitro, dutasteride is metabolised by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite.

Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged 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.

The elimination of dutasteride is dose dependent and the process appears to be described by two elimination pathways in parallel, one that is saturable at clinically relevant concentrations and one that is non saturable. 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 therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower, linear elimination pathway is dominating and the half-life is approx. 3-5 weeks.

Tamsulosin

Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged active substance. The plasma elimination half-life has been reported to be between 4 and 5.5 hours.

Elderly

Dutasteride

Dutasteride pharmacokinetics 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. No significant influence of age was seen on the exposure of dutasteride but the half-life was shorter in men under 50 years of age. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old.

Tamsulosin

Increased age diminishes the intrinsic clearance of tamsulosin, which results in slightly prolonged disposition of the drug in elderly patients. The elimination half-life of the modified release tamsulosin 0.4 mg is estimated to be 14 to 15 hours in elderly patients.

After a single dose of tamsulosin 0.4 mg in the fed state, plasma levels of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, Cmax in patients is about two thirds higher than that reached after a single dose. Although this was seen in elderly patients, the same finding would also be expected in young ones.

Renal impairment

Dutasteride

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no clinically significant increase of the dutasteride plasma concentrations is anticipated for patients with renal impairment (see section 4.2).

Tamsulosin

The treatment of severely renal impaired patients (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied.

Hepatic impairment

Dutasteride

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see section 4.3). Because dutasteride is eliminated mainly through metabolism the plasma levels of dutasteride are expected to be elevated in these patients and the half-life of dutasteride be prolonged (see section 4.2 and section 4.4).

Tamsulosin

No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see also section 4. 3).

5.3 Preclinical safety data

There have not been conducted Non-clinical studies with Dutasteride/Tamsulosin Rowa. The following information is available on the individual components:

Dutasteride

Current studies of general toxicity, genotoxicity and carcinogenicity did not show any particular risk to humans.
Reproduction toxicity studies in male rats have shown a decreased weight of the prostate and seminal vesicles, decreased secretion from accessory genital glands and a reduction in fertility indices (caused by the pharmacological effect of dutasteride). The clinical relevance of these findings is unknown.

As with other 5 alpha reductase inhibitors, feminization of male foetuses in rats and rabbits has been noted when dutasteride was administered during gestation. Dutasteride has been found in blood from female rats after mating with dutasteride treated males. When dutasteride was administered during gestation to primates, no feminization of male foetuses was seen at blood exposures sufficiently in excess of those likely to occur via human semen. It is unlikely that a male foetus will be adversely affected following seminal transfer of dutasteride.

Tamsulosin

Studies of general toxicity and genotoxicity did not show any particular risk to humans other than those related to the pharmacological properties of tamsulosin.

Tamsulosin hydrochloride produced no evidence of mutagenic potential in vitro in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells. There were no mutagenic effects in the in vivo sister chromatid exchange and mouse micronucleus assay

A study examined the antifertility effects of tamsulosin, a highly potent and a selective alpha 1-adrenoceptor antagonist on male rats. The drug was administered subcutaneously as a single dose (0.15 mg kg^{-1}). The drug caused a significant reduction in fertility (measured by number of uterine implants, quantal pregnancy, and fertility index). The antifertility effect was short lived and rapid in both onset (no later than seven hours of administration) and recovery (within seven days). Libido and mating performance remained essentially uninhibited. On the other hand, the antifertility effect was accompanied by significant impairment in ejaculatory competence and enhancement of pre-implantation losses. Based on the results of this study and our previous studies, it is concluded that α1-adrenoceptor blockade has a potent antifertility effect in male rats.

Studies in female rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin hydrochloride, respectively. In female rats, the reductions in fertility after single

doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard Capsule Shell:
Black iron oxide (E172)
Red iron oxide (E172)
Titanium Dioxide (E171)
Yellow iron Oxide (E172)
Gelatin.

Capsule contents:
Propylene Glycol Monocaprylate
Butylhydroxytoluene (E321).

Capsule shell:
Gelatin
Glycerol
Titanium dioxide (E171)
Triglycerides (medium chain)
Lecithin (may contain soya oil).

Tamsulosin Pellets:
Methacrylic acid - ethyl acrylate copolymer 1:1 dispersion 30 per cent
Cellulose Microcrystalline
Dibutyl Sebacate
Polysorbate 80
Silica colloidal anhydrous
Calcium stearate

Black Inks: Shellac
Black Iron Oxide (E172)
Propylene Glycol
Strong ammonia solution
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

HDPE bottle with silica gel desiccant contained in the cap

7 hard capsules in 35 ml bottle
30 hard capsules in 100 ml bottle
90 hard capsules in 250 ml bottle
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dutasteride is absorbed through the skin, therefore contact with leaking capsules must be avoided. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water (see section 4.4).

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/076/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2020

10 DATE OF REVISION OF THE TEXT