Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dutasteride/Tamsulosin Hydrochloride 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).

Excipients with known effect
Each capsule contains lecithin (which may contain soya oil) and sunset yellow FCF (E 110). Each capsule contains ≤ 0.1 mg sunset yellow FCF.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Oblong, around 24 mm length, hard capsules with a brown body and an orange cap.

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

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 (including elderly)
The recommended dose of Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules is one capsule (0.5 mg/ 0.4mg) once daily.

Where appropriate, Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules may be used to substitute concomitant dutasteride and tamsulosin hydrochloride in existing dual therapy to simplify treatment.

Where clinically appropriate, direct change from dutasteride or tamsulosin hydrochloride monotherapy to Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules may be considered.

Renal impairment
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).

Hepatic impairment
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 Hydrochloride 0.5mg/0.4mg hard capsules is contraindicated (see section 4.3).

Paediatric population
Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules is contraindicated in the paediatric population (under 18 years of age) (see section 4.3).

Method of administration

For oral use.

Patients should be instructed to swallow the capsules whole, approximately 30 minutes after the same meal each day. The capsules should not be 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 Hydrochloride 0.5mg/0.4mg hard capsules 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.

Prostate cancer and high grade tumours
The REDUCE study, a 4-year, multicentre, randomised, double-blind, placebo controlled study investigated the effect of dutasteride 0.5 mg daily on patients with a high risk for prostate cancer (including men 50 to 75 years of age with PSA levels of 2.5 to 10 ng/ml and a negative prostate biopsy 6 months before study enrolment) compared to placebo. Results of this study revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men (n=29, 0.9%) compared to placebo (n=19, 0.6%). The relationship between dutasteride and Gleason 8 - 10 prostate cancers is not clear. Thus, men taking Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules should be regularly evaluated for prostate cancer (see section 5.1).

Prostate specific antigen (PSA)
Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment.

Patients receiving Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules should have a new PSA baseline established after 6 months of treatment with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules may signal the presence of prostate cancer or noncompliance to therapy with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-alpha 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 Hydrochloride 0.5mg/0.4mg hard capsules does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established.

Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules therapy, no adjustment to its value appears necessary.

Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients prior to initiating therapy with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules and periodically thereafter.

Cardiovascular adverse events
In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was marginally higher among subjects taking the combination of dutasteride and an alpha1-adrenoceptor antagonist, primarily tamsulosin, than it was among subjects not taking the combination. However, the incidence of cardiac failure in these trials was lower in all actively treated groups compared to the placebo group, and other data available for dutasteride or alpha1-adrenoceptor antagonists do not support a conclusion on increased cardiovascular risks (see section 5.1).

Breast neoplasia
There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-alpha reductase inhibitors (see section 5.1). Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

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

Hypotension
Orthostatic: As with other alpha1- adrenoceptor antagonists, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved.

In order to minimise the potential for developing postural hypotension the patient should be haemodynamically stable on an alpha1- adrenoceptor antagonist prior to initiating use of PDE5 inhibitors.
Symptomatic: Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors (e.g. sildenafil, tadalafil, vardenafil). Alpha1- adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension (see section 4.5).

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 increase the risk of eye complications during and after the operation. The initiation of therapy with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules 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 Hydrochloride 0.5mg/0.4mg hard capsules 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 and CYP2D6
Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 (e.g. ketoconazole), or to a lesser extent, with strong inhibitors of CYP2D6 (e.g. paroxetine) can increase tamsulosin exposure (see section 4.5). Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor, a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

Hepatic impairment
Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules has not been studied in patients with liver disease. Caution should be used in the administration of Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules to patients with mild to moderate hepatic impairment (see section 4.2, section 4.3 and section 5.2).

Excipients
This medicinal product contains the colouring agent sunset yellow FCF (E110), which may cause allergic reactions.

This medicinal product contains lecithin derived from soya oil. If you are allergic to peanut or soya, do not use this medicinal product (see section 4.3).

This medicinal product 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 interaction

There have been no drug interaction studies for Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules. The following statements reflect the information 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
Dutasteride is mainly eliminated via metabolism. *In vitro* studies indicate that this metabolism is catalysed 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 pharmacodynamic 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
Concomitant administration of tamsulosin hydrochloride with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other alpha1- adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride/Tamsulosin should not be used in combination with other alpha1- adrenoceptor antagonists.

Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8 respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor. The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure (see section 4.4).

Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every six hours for six 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.

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. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

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

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

4.6 Fertility, pregnancy and lactation

Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules is contraindicated for use by women. There have been no studies to investigate the effect of Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules on pregnancy, lactation and fertility. The following statements reflect the information 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 foetus, inhibit the development of the external genitalia of the foetus (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 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).

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 foetal harm.

For information on preclinical data, see section 5.3.

Breast-feeding
It is not known whether dutasteride or tamsulosin are 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.

Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

4.7 Effects on ability to drive and use machines

No studies on the effects of Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules on the ability to drive and use machines have been performed. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules.

4.8 Undesirable effects

The data presented here relate to the co-administration of dutasteride and tamsulosin from the 4 year analysis of the CombAT (Combination of Avodart and Tamsulosin) study, a comparison of dutasteride 0.5mg and tamsulosin 0.4mg once daily for four years as co-administration or as monotherapy. Bioequivalence of the combination Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules with the reference combination of dutasteride and tamsulosin has been demonstrated (see section

5.2). Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) is also provided. Note that not all the adverse events reported with the individual components have been reported with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules and these are included for information for the prescriber.
Data from the 4 year CombAT study 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 co-administration 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 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 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, BPH monotherapy clinical studies and REDUCE study are shown in the table below.
In addition the undesirable effects for tamsulosin below are based on information available in the public domain. The frequencies of adverse events 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 Reaction**	**Dutasteride + Tamsulosin[a]**	**Dutasteride**	**Tamsulosin[c]**
Nervous System Disorders	Syncope	-	-	Rare
	Dizziness	Common	-	Common
	Headache	-	-	Uncommon
Cardiac Disorders	Cardiac Failure (Composite term[1])	Uncommon	Uncommon[d]	-
	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
	Pruritus	-	-	Uncommon
Reproductive System and Breast Disorders	Priapism	-	-	Very Rare
	Impotence[3]	Common	Common[b]	-
	Altered (decreased) libido[3]	Common	Common[b]	-
	Ejaculation disorders[3] ^	Common	Common[b]	Common
	Breast Disorders[2]	Common	Common[b]	-
General Disorders and Administration Site Disorders	Asthenia	-	-	Uncommon

[a]. Dutasteride + tamsulosin: from CombAT study - the frequencies of these adverse events decrease over time of treatment, from year 1 to year 4.
[b]. Dutasteride: from BPH monotherapy clinical studies.
[c]. Tamsulosin: from EU Core Safety Profile for tamsulosin.
[d]. 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.
[^]. 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, impacted 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, localised oedema, 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
During postmarketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha1- adrenoceptor antagonists, including tamsulosin (see section 4.4).

In addition atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative, ejaculation disorder, retrograde ejaculation, ejaculation failure and dry mouth have been reported in association with tamsulosin use. The frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +3531 6767836; Website: www.hpra. ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No data are available with regard to overdosage of Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules. 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 overdosage symptomatic and supportive treatment should be given as appropriate.

Tamsulosin
Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed which were treated with fluid replacement and the patient could be discharged the

same day. 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.

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 α_{1a} and α_{1d} adrenoreceptors. These drugs have complementary mechanisms of action that rapidly improve symptoms, urinary flow and reduce the risk of acute urinary retention (AUR) and the need for BPH related surgery.

Dutasteride inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for prostate growth and BPH development. Tamsulosin inhibits $_{\alpha 1a}$ and $_{\alpha 1d}$ 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.

Dutasteride co-administration with tamsulosin

The following statements reflect the information available on dutasteride and tamsulosin co-administration therapy.

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 ^{3}30ml and a PSA value within the range 1.5 - 10 ng/mL in a 4 year multicentre, multinational, randomized double-blind, parallel group study. Approximately 53% of subjects had previous exposure to 5-alpha reductase inhibitor or alpha1- adrenoceptor antagonist. 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 (Q_{max}) and prostate volume. The combination achieved significance for IPSS from Month 3 compared to dutasteride and from Month 9 compared to tamsulosin. For Q_{max} combination achieved significance from Month 6 compared to both dutasteride and tamsulosin.

The combination of dutasteride and tamsulosin provides superior improvement in symptoms than either component alone. After 2 years of treatment, co-administration therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of -6.2 units.

The adjusted mean improvement in flow rate from baseline was 2.4 ml/sec for co-administration therapy, 1.9 ml/sec for dutasteride and 0.9 ml/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for co-administration therapy, -1.7 for dutasteride and -1.5 for tamsulosin.
These improvements in flow rate and BII were statistically significant for co-administration therapy compared to both monotherapies.

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

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 incidende 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 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 ³4 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 (Q_{max}) 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
Q_{max} (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
PBH 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 (PBH-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 ³4 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

Dutasteride
Dutasteride 0.5 mg/day or placebo was evaluated in 4325 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 (Q_{max}) 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 approx. 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.

Q_{max} (maximum urine flow):
Mean baseline Q_{max} for the studies was approx 10 ml/sec (normal Q_{max} ³ 15 ml/sec). After one and two year 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 doubleblind 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 against 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's 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 3374 patient years of exposure to dutasteride, and at the time of registration in the 2-year open label extension, there were 2 cases of male 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 17489 patient years exposure to dutasteride and 5027 patient years exposure to dutasteride and tamsulosin combination there were no cases of breast cancer reported in any treatment groups.

Two case control, epidemiological studies, one conducted in a US (n=339 breast cancer cases and n=6,780 controls) and the other in a UK (n=398 breast cancer cases and n=3,930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5 ARIs (see section 4.4). Results from the first study did not identify a positive association for male breast cancer (relative risk for ^{3} 1 year of use before breast cancer diagnosis compared with < 1 year of use: 0.70: 95% CI 0.34, 1.45). In the second study, the estimated odds ratio for breast cancer associated with the use of 5 ARIs compared with non-use was 1.08: 95% CI 0.62, 1.87).

A causal relationship between the occurrence of male breast cancer and long term use of dutasteride has not been established.

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.

Cardiovascular adverse events:
In a 4 year BPH study of dutasteride in combination with tamsulosin in 4844 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, (4/1623, 0.2%) and tamsulosin, (10/1611, 0.6%).

In a separate 4-year study 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), 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 alpha1-adrenoceptor antagonist concomitantly (12/1152, 1.0%), compared to subjects taking dutasteride and no alpha1- adrenoceptor antagonist (18/2953, 0.6%), placebo and an alpha1- adrenoceptor antagonist (1/1399, <0.1%), or placebo and no alpha1-adrenoceptor antagonist (15/2727, 0.6%).

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18,802) that evaluated the risks of developing cardiovascular adverse events from the use of dutasteride (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1.05; 95% CI 0.71, 1.57), acute myocardial infarction (RR 1.00; 95% CI 0.77, 1.30) or stroke (RR 1.20; 95% CI 0.88, 1.64) were found.

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 the men at risk of prostate cancer. The percentatge of subjects diagnosed with Gleason 8-10 cancers was consistent with 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 percentatge of subjects diagonsed 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).

The additional 2-year follow-up study of the REDUCE trial did not identify any new cases of Gleason 8–10 prostate cancers.

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.

Four different epidemiological, population-based studies (two of which were based on a total population of 174,895, one on a population of 13,892, and one on a population of 38,058) showed that the use of 5-alpha reductase inhibitors is not associated with the occurrence of high grade prostate cancer, nor with prostate cancer, or overall mortality.

The relationship between dutasteride and high grade prostate cancer is not clear.

Effects on sexual function:
The effects of Dutasteride/Tamsulosin on sexual function were assessed in a double-blind, placebo-controlled study in sexually active men with BPH (n=243 Dutasteride-tamsulosin GSK, n=246 placebo). A statistically significant (p<0.001) greater reduction (worsening) in the Men's Sexual Health Questionnaire (MSHQ) score was observed at 12 months in the combination group. The reduction was mainly related to a worsening of the ejaculation and overall satisfaction domains rather than the erection domains. These effects did not affect sutdy participants' perception of Dutasteride/Tamsulosin, which was rated with a statistically significant greater satisfaction throughout 12 months compared with placebo (p<0.05). In this study the sexual adverse events occurred during the 12 months of treatment and approximately half of these resolved within 6-month post-treatment.

Dutasteride/Tamsulosin combination and dutasteride monotherapy are known to cause sexual function adverse effects (see section 4.8).

As observed in other clinical studies, including CombAT and REDUCE, the incidence of adverse events related to sexual function decreases over time with continued therapy.

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

Bioequivalence was demonstrated between dutasteride-tamsulosin and concomitant dosing with separate dutasteride and tamsulosin capsules.

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
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 Hydrochloride 0.5mg/0.4mg hard capsules 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 C_{max} 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 (C_{ss}) 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 0.2l/kg).

Biotransformation

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.

Tamsulosin
There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolised by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. In vitro results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolising enzymes may lead to increased exposure to tamsulosin (see section 4.4 and 4.5). The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Elimination

Dutasteride
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.

Following intravenous or oral administration of an immediate-release formulation, the elimination half life of tamsulosin in plasma ranges from 5 to 7 hours. Due to the absorption rate-controlled pharmacokinetics with tamsulosin modified release capsules, the apparent elimination half life of tamsulosin in the fed state is approximately 10 hours and in the steady state is approximately 13 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
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 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 pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CLcr < 70$ mL/min/1.73m2) or moderate-severe ($10 \leq CLcr < 30$ mL/min/1.73m2) renal impairment and 6 normal subjects ($CLcr > 90$ mL/min/1.73m2). 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 endstage renal disease ($CLcr < 10$ mL/min/1.73m2) 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
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.

5.3 Preclinical safety data

Non-clinical studies have not been conducted with Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules. Dutasteride and tamsulosin hydrochloride individually have been extensively evaluated in animal toxicity tests and findings were consistent with the known pharmacological actions of 5 alpha-reductase inhibitors and alpha1- adrenoceptor antagonists. The following statements reflect the information 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, feminisation 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 feminisation 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.

In carcinogenicity studies in rats and mice, tamsulosin hydrochloride produced an increased incidence of proliferative changes of the mammary glands in females. These findings, which are probably mediated by hyperprolactinaemia and only occurred at high dose levels, are regarded as not clinically relevant.

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 on sperm counts or sperm function have not been evaluated.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard Capsule Shell:
Hypromellose
Carrageenan (E407)
Potassium Chloride
Titanium Dioxide (E171)
Iron Oxide Red (E172)
Sunset Yellow FCF (E110)

Contents in Dutasteride Soft Capsule:
Content in the Capsule:
Glycerol monocaprylocaprate

Butylhydroxytoluene (E321)

Soft Capsule Shell:
Gelatin
Glycerol
Titanium Dioxide (E171)
Iron Oxide Yellow (E172)
Triglycerides, medium chain
Lecithin (may contain soya oil) (E322)

Tamsulosin Pellets:
Cellulose, microcrystalline
Methacrylic acid-ethyl acrylate copolymer 1:1 dispersion 30%
Methacrylic acid-ethyl acrylate copolymer 1:1
Magnesium stearate
Sodium hydroxide
Triacetin
Talc
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

For HPDE bottles, do not use longer than 6 weeks for 30 capsules packsize and longer than 18 weeks for 90 capsules packsize, after first opening.

6.4 Special precautions for storage

Do not store above 30 ºC.

6.5 Nature and contents of container

High Density PolyEthylene (HDPE) bottles, sealed with aluminium foil with polypropylene child-resistant closures.

Aluminium/aluminium blisters.

They are available in packs of 7, 28, 30 and 90 capsules placed in either HDPE bottles or in aluminium/aluminium blisters.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd November 2019
Date of last renewal: 6th September 2024

10 DATE OF REVISION OF THE TEXT

February 2025