1. Name of the Medicinal Product
TAMREL-D

2. Qualitative and quantitative composition
Each hard gelatin capsule contains:
Tamsulosin hydrochloride USP.....0.4.mg
(as sustained release pellets)

Dutasteride USP.....0.5 mg

(as plain pellets form)

Excipients .....q.s.

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Solid dosage form (Capsules)
Hard gelatin filled capsules with size "1", Deep blue colour cap & Clear transparent body containing off white & sunset yellow-colored spherical pellets.

4. Clinical particulars:
4.1 Therapeutic indications:

It is indicated in:

-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.

4.2 Posology and method of administration
Adults (including elderly)
The recommended dose is one capsule (0.5 mg/ 0.4 mg) taken orally approximately 30 minutes after the meals each day. The Capsules should be swallowed whole and not chewed or opened. Contacts with the contents of the dutasteride capsule contained within the hard-shell capsule may result in the irritation of the oropharyngeal mucosa.
Where appropriate it may be used to substitute concomitant dutasteride and tamsulosin hydrochloride existing dual therapy to simplify treatment.
Where clinically appropriate direct change from dutasteride or tamsulosin hydrochloride monotherapy to TAMREL-D 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.
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. In patients with severe hepatic impairment, the use of TAMREL-D is contraindicated.

4.3 CONTRA-INDICATIONS:

It is contraindicated in:

-women and children and adolescents

- patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin (including tamsulosin-induced angio-edema), soya, peanut or any of the other excipients
-patients with a history of orthostatic hypotension
-patients with severe hepatic impairment.

4.4 Special warning and special precaution 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

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

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 TAMREL-D and periodically thereafter.

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

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

In the interpretation of a PSA value for a patient taking TAMREL-D, previous PSA values while on dutasteride treatment should be sought for comparison.

Treatment with TAMREL-D 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 TAMREL-D. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing TAMREL-D 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 TAMREL-D should be regularly evaluated for prostate cancer risk including PSA testing.

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

Orthostatic: As with other alpha-blockers, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with TAMREL-D

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 alpha-blocker therapy prior to initiating use of PDE5 inhibitors.
Symptomatic: Caution is advised when alpha adrenergic blocking agents including tamsulosin are

coadministered with PDE5 inhibitors (e.g. sildenafil, tadalafil, vardenafil). Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

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 TAMREL-D 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 TAMREL-D 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 Capsule

Dutasteride is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking capsules. 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. Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a strong (e.g., paroxetine) CYP2D6 inhibitor.
Tamsulosin hydrochloride should be used with caution in patients taking a moderate CYP3A4 inhibitor (e.g. erythromycin) in combination with either strong (e.g. paroxetine) or moderate (e.g. terbinafine) CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

Hepatic impairment

TAMREL-D has not been studied in patients with liver disease. Caution should be used in the administration of TAMREL-D to patients with mild to moderate hepatic impairment.

Breast neoplasia

Breast cancer has been reported in men taking dutasteride in clinical trials 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.

4.5 Interaction with FPPs and other forms of interaction

There have been no drug interaction studies for TAMREL-D. 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,

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 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 alpha-1 adrenergic blockers could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other alpha1 adrenergic blockers.

Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the Cmax 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 Cmax 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 coadministration 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.).

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. 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, amitriptyline, 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.
No interactions at the level of hepatic metabolism have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolising enzyme system), involving amitriptyline, salbutamol and glibenclamide. Diclofenac however, may increase the elimination rate of tamsulosin.
In patients taking metronidazole, the assay of aspartate amino transferase may give spuriously low values: this depends on the method used.
Potentiation of warfarin-type (but not heparin) anticoagulant therapy has been reported so that dose adjustment of the anticoagulant may be needed.
Lithium retention with evidence of possible renal damage has been reported where this compound and metronidazole have been used concurrently. Preferably, apart from monitoring lithium, creatinine and electrolyte concentrations, lithium therapy should be tapered and/or withdrawn before use of metronidazole. Cimetidine inhibits the metabolism of metronidazole causing an increase in plasma metronidazole concentrations.

4.6 Pregnancy and Lactation:
TAMREL-D is contraindicated for use by women. There have been no studies to investigate the effect of TAMREL-D on pregnancy, lactation and fertility. The following statements reflect the information available from studies with the individual components
Fertility
Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men . The possibility of reduced male fertility cannot be excluded.
Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.
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. 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
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.
Lactation

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

4.7 Effects on ability to drive and use machines

No studies on the effects of TAMREL-D 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 TAMREL-D.

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 TAMREL-D with co-administered dutasteride and tamsulosin has been demonstrated. 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 TAMREL-D 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 as 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.

a. Dutasteride + tamsulosin: from CombAT study - the frequencies of these adverse

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

events decrease over time of

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

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.

OTHER DATA

The REDUCE study revealed a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo .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 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 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 post marketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a Variant of Small pupil syndrome, during cataract surgery have been associated with alpha-1 blocker therapy, including tamsulosin

In addition atrial fibrillation, arrhythmia, tachycardia and dyspnoea 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
Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose
No data are available with regard to overdosage of TAMREL-D.. 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 diarrhea 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 α1a and α1dadrenoreceptors. 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 α1aand α1dadrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α1-receptors in the prostate are of the α1asubtype.

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 Cmax was observed for the tamsulosin component of dutasteride tamsulosin in the fed state compared to the fasted state. Food had no $_{\text{effect}}$ 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 C 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 0.2l/kg).

Metabolism

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. 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 range from 5 to 7 hours. Because of 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 in patients 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

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate

(30 ≤ CLcr < 70 mL/min/1.73m2) or moderate-severe (10 ≤ 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. 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

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.

6. Pharmaceutical particulars

6.1 List of excipients

Not Applicable

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry place, below 30° C. Protect from Light.

Keep away from the reach of Children**.**

6.5 Nature and contents of container

10 Capsules are packed in Alu-Alu Strip and such 3 Strips are packed in carton along with pack insert**.**

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing Authorisation holder

Cachet Pharmaceuticals Pvt. Ltd.

Village - Thana, Baddi, Distt.-Solan, Himachal Pradesh

415, Shah Nahar, Worli, Mumbai 400 018.

India.

8. Marketing authorization number

H2025/CTD10485/23737

9. Date of first authorization/renewal of the authorization

2025 March 06

10. Date of revision of the text

2025 March 06