1.6 PRODUCT INFORMATION

1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

D-TAM TABLETS

Active Ingredient(s) (INN or Scientific name): Tamsulosin 0.4 mg and Dutasteride 0.5 mg

Dosage Form and sub-form: TABLETS

Strength: Tamsulosin 0.4 mg and Dutasteride 0.5 mg

Route of Administration: Oral

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Tamsulosin 0.4mg

Dutasteride 0.5 mg

Batch size: 0.25L

Sr. No.	Raw material	SPF	Qty in mg	% Overage	Qty in Kg
1	Tamsulosin (2%)	BP	0.40	02%	0.010
2	Maize Starch	BP	21.10	NA	0.528
3	lactose Monohydrate	BP	46.0	NA	1.150
4	Polysorbate 80	BP	0.20	NA	0.005
5	PVPK 30 BP	BP	2.50	NA	0.063
6	Sodium Starch Glycolate	BP	0.36	NA	0.009
7	Dutasteride	IH	0.50	NA	0.013
8	lactose Monohydrate	BP	79.0	NA	1.975
9	Microcrystalline Cellulose	BP	37.15	NA	0.929
10	Pregelatinised starch	BP	21.25	NA	0.531
11	Sodium Lauryl Sulphate	BP	0.3.	NA	0.008
12	Sodium Starch Glycolate	BP	6.00	NA	0.150
13	Magnesium Stearate	BP	1.30	NA	0.033
14	Titanium Dioxide	BP	7.50	NA	0.188
15	Isopropyl Alcohol	BP	74.6	NA	1.865

16	Methylene Chloride	BP	82.8	NA	2.070
17	Insta Glow	IH	0.23	NA	0.006
18	Isopropyl Alcohol BP	BP	1.60	NA	0.040
19	Methylene Chloride BP	BP	3.20	NA	0.080

Abbreviation: BP: British Pharmacopoeia, IH: In House Specification

3. PHARMACEUTICAL FORM

Tablet.

White to off white coloured, circular, film coated tablets plain on Both sides

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

D-TAM indicated for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate

4.2 Posology and method of administration

Adults (including elderly)

The recommended dose is one tablet (Tamsulosin 0.4mg and Dutasteride 0.5 mg) once daily.

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 D-TAM is contraindicated.

4.3 Method of administration

Oral Administration

4.4 Contraindications

Hypersensitivity to the active substance or to any of the Excipients.

D-TAM is contraindicated in:

- women and children and adolescents,
- patients with a history of orthostatic hypotension.
- patients with severe hepatic impairment.

4.5 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 D-TAM should be regularly evaluated for prostate cancer.

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

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

Treatment with D-TAM 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 D-TAM. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing D-TAM 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 D-TAM 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 alpha$_1$ - 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 alpha$_1$-adrenoceptor antagonists do not support a conclusion on increased cardiovascular risks.

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. 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 alpha$_1$- 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 D-TAM 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 alpha$_1$ - 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). Alpha$_1$ - 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.

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 D-TAM 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 D-TAM 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.

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

4.6 Paediatric population

Dutasteride-tamsulosin is contraindicated in the paediatric population (under 18 years of age)

4.7 Interaction with other medicinal products and other forms of interaction

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 alpha$_1$- adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other alpha$_1$- adrenoceptor antagonists.

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 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.

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.

4.8 Pregnancy and Lactation

D-TAM is contraindicated for use by women. There have been no studies to investigate the effect of D-TAM on pregnancy, lactation and fertility. The following statements reflect the information available from studies with the individual components

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 (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.

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. The possibility of reduced male fertility cannot be excluded.

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

4.9 Effects on ability to drive and use machines

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

4.10 Undesirable effects

The most common adverse reactions, reported in ≥1% of patients, treated with coadministered dutasteride and tamsulosin are ejaculation disorders, impotence, decreased libido, dizziness, and breast disorders.

4.11 Overdose

No data are available with regard to overdosage of D-TAM. 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

Mechanism of action

D-TAM (Dutasteride/Tamsulosin) is a combination of two drugs with complementary mechanisms of action to improve symptoms in patients with Benign Prostatic Hyperplasia (BPH): dutasteride, a dual 5alpha-reductase inhibitor (5ARI) and Tamsulosin hydrochloride, an antagonist of alpha1A-adrenoreceptors.

Dutasteride: Selective type I and II 5α-reductase inhibitor; inhibits conversion of testosterone to dihydrotestosterone, the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland.

Tamsulosin: α1A antagonist; selective blockade of α1 adrenoceptors in the prostate results in relaxation of the smooth muscles of the bladder neck and prostate, improving urine flow rate and reducing BPH symptoms.

5.2 Pharmacokinetic properties

Absorption

Dutasteride: Absolute bioavailability (60%); Cmax=2.14ng/mL, Tmax=3 hrs, AUC=39.6ng•hr/mL.

Tamsulosin: Complete; Cmax=11.3ng/mL, Tmax=6 hrs, AUC=187.2ng•hr/mL.

Distribution

Dutasteride: V_d=300-500L, plasma protein binding (99% albumin, 96.6% α-1 acid glycoprotein).

Tamsulosin: Plasma protein binding (94-99%); (IV) V_d=16L.

Metabolism:

Dutasteride: Extensively metabolized by CYP3A4/3A5 produced 4'-hydroxydutasteride, 1,2-dihydroxydutasteride, 6-hydroxydutasteride (major metabolites).

Tamsulosin: Extensively metabolized by CYP3A4, CYP2D6 in Liver.

Elimination:

Dutasteride: Urine (<1% unchanged), feces (5% unchanged, 40% metabolites); $T_{1/2}$=5 weeks.

Tamsulosin: Urine (76%, <10% unchanged), feces (21%); $T_{1/2}$=14-15 hrs, 9-13 hrs

5.3 Preclinical safety data

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 alpha$_1$ - 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

- Maize Starch BP

- lactose Monohydrate
- Polysorbate 80 BP
- PVPK 30 BP
- Sodium Starch Glycolate BP
- Microcrystalline Cellulose BP
- Pregelatinised starch BP
- Sodium Lauryl Sulphate BP
- Magnesium Stearate BP
- Titanium Dioxide BP
- Isopropyl Alcohol BP
- Methylene Chloride BP
- Insta Glow IH

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30ºC, Protect from light & Moisture, Keep medicines out of reach of children.

6.5 Nature and contents of container

3 X 10 Tablet are packed in carton along with product insert.

7. MARKETING AUTHORISATION HOLDER

Star Biotech Limited

Address: 1st floor, Prestige House, Rwandex, Kigali-Rwanda

Telephone: (+250) 785377688 / (+250) 787229914

Email: shantilal.bhanderi@yahoo.com