National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

DUTASTERIDE AND TAMSULOSIN TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated Tablet Contains:

Tamsulosin hydrochloride BP	
Eq. to Tamsulosin	0.4 mg
Dutasteride BP	0.5 mg
Excipients	Q.S

Colour: Red oxide of iron

3. PHARMACEUTICAL FORM

Oral film coated tablets

4. Clinical particulars

4.1 Therapeutic indications

Tamsulosin Hydrochloride and Dutasteride tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. The tablets are not intended for use as an anti-hypertensive drug.

Dutasteride is not approved for the prevention of prostate cancer.

4.2 Posology and method ofadministration

The recommended dose of DUTASTERIDE AND TAMSULOSIN TABLETS is one tablet once daily with or without food. The tablet should be swallowed whole and should not be crushed or chewed. No dosage adjustment is required for subjects with renal impairment or for the elderly.

Method of administration

Tablets for oral administration.

4.3 Contraindications

DUTASTERIDE AND TAMSULOSIN TABLETS are contraindicated for use in women of childbearing potential and during pregnancy.
DUTASTERIDE AND TAMSULOSIN TABLETS are contraindicated for use in paediatric patients.
DUTASTERIDE AND TAMSULOSIN TABLETS are contraindicated for patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to dutasteride or other 5 alpha-reductase inhibitors, tamsulosin hydrochloride or to any component of the DUTASTERIDE AND TAMSULOSIN TABLETS.

4.4 Special warnings and precautions for use

Evaluation of Other Urological Diseases

Prior to initiating treatment with DUTASTERIDE AND TAMSULOSIN TABLETS, consideration should be given to other urological conditions that may cause similar symptoms. In addition, BPH and prostate cancer may coexist.

Orthostasis

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in tamsulosin hydrochloride treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents, there is a potential risk of syncope. Patients beginning treatment with DUTASTERIDE AND TAMSULOSIN TABLETS should be cautioned to avoid situations in which injury could result should syncope occur.

Increased Risk of High-grade Prostate Cancer

In men aged 50 to 75 years, with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL, who were taking dutasteride in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (dutasteride 1.0% versus placebo 0.5%).

Effect on Semen Characteristics

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 years (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.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 Inhibitors

No clinical drug interaction trials have been performed to evaluate the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics. However, based on in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, troleandomycin, and ciprofloxacin.

Cimetidine

The effects of cimetidine at the highest recommended dose (400 mg every 6 hours for 6 days) on the pharmacokinetics of tamsulosin hydrochloride 0.4 mg dose was investigated in 10 healthy volunteers (age range: 21 to 38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin hydrochloride, which resulted in a moderate increase in the tamsulosin hydrochloride AUC (44%). Therefore, DUTASTERIDE AND TAMSULOSIN TABLETS should be used with caution in combination with cimetidine.

Digoxin and Theophylline

Dosage adjustments are not necessary when tamsulosin hydrochloride is administered concomitantly with digoxin or theophylline. Dutasteride does not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Furosemide

The pharmacokinetic and pharmacodynamic interaction between tamsulosin hydrochloride 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in 10 healthy volunteers (age range: 21 to 40 years). Tamsulosin hydrochloride had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11-12% reduction in tamsulosin hydrochloride Cmax and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin hydrochloride dosage.

Calcium Channel Antagonists

In a population pharmacokinetics analysis, a decrease in clearance of dutasteride was noted when coadministered with the CYP3A4 inhibitors verapamil (-37%, n=6) and diltiazem (-44%, n=5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was coadministered with dutasteride (+7%, n=4). The decrease in clearance and subsequent increase in exposure to dutasteride in the presence of verapamil and diltiazem is not considered to be clinically significant. The change in dutasteride exposure is not considered to be clinically significant. No dosage adjustment of dutasteride is recommended.

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

4.6 Pregnancy and Lactation

These tablets are not indicated for use.

4.7 Effects on ability to drive and use machines

There are no data available.

4.8 Undesirable effects

Adverse Reaction	Adverse Reaction Time of Onset				
	Year 1		Year 2	Year 3	Year 4
	Months 0-6	Months 7-12			
Co-administrationa Dutasteride Tamsulosin	(n=1,610) (n=1,623) (n=1,611)	(n=1,527) (n=1,548) (n=1,545)	(n=1,428) (n=1,464) (n=1,468)	(n=1,283) (n=1,325) (n=1,281)	(n=1,200) (n=1,200) (n=1,112)
Ejaculation disordersb,c Co-administration Dutasteride Tamsulosin	7.8% 1.0% 2.2%	1.6% 0.5% 0.5%	1.0% 0.5% 0.5%	0.5% 0.2% 0.2%	<0.1% 0.3% 0.3%
Impotencec, d Co-administration Dutasteride Tamsulosin	5.4% 4.0% 2.6%	1.1% 1.1% 0.8%	1.8% 1.6% 1.0%	0.9% 0.6% 0.6%	0.4% 0.3% 0.1%
Decreased libidoc, e Co-administration Dutasteride Tamsulosin	4.5% 3.1% 2.0%	0.9% 0.7% 0.6%	0.8% 1.0% 0.7%	0.2% 0.2% 0.2%	0.0% 0.0% <0.1%
Breast disordersf Co-administration Dutasteride Tamsulosin	1.1% 0.9% 0.4%	1.1% 0.9% 0.4%	0.8% 1.2% 0.4%	0.9% 0.5% 0.2%	0.6% 0.7% 0.0%
Dizziness Co-administration Dutasteride Tamsulosin	1.1% 0.5% 0.9%	0.4% 0.3% 0.5%	0.1% 0.1% 0.4%	<0.1% <0.1% <0.1%	0.2% <0.1% 0.0%

4.9 Overdose

Overdosage with DUTASTERIDE AND TAMSULOSIN TABLETS could potentially lead to hypotension due to the tamsulosin hydrochloride component. In case of hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94-99% protein bound; therefore, dialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Tamsulosin Hydrochloride

Mechanism of action

Tamsulosin hydrochloride, an alpha1-adrenoceptor blocking agent, exhibits selectivity for alpha1-receptors in the human prostate. At least three discrete alpha1-adrenoceptor subtypes have been identified: alpha1A, alpha1B and alpha1D; their distribution differs between human organs and tissue. Approximately 70% of the alpha1-receptors in the human prostate are of the alpha1A subtype. Blockade of these adrenoreceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in the urine flow rate and a reduction in the symptoms of BPH.

Dutasteride

Mechanism of action

Dutasteride inhibits the conversion of testosterone to 5 alpha-dihydrotestosterone (DHT) by a competitive and specific inhibition of both the type I and type II isoforms of steroid 5 alpha-reductase (5AR). Testosterone is converted to DHT by the enzyme 5 alpha-reductase, which exists as 2 isoforms, type I and type II. The type II isoenzyme is primarily active in the reproductive tissues, while the type I isoenzyme is also responsible for testosterone conversion in the skin and liver. DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland.

5.2 Pharmacokinetic properties

Tamsulosin Hydrochloride

Absorption: Absorption of tamsulosin hydrochloride is essentially complete (>90%), following oral administration under fasting conditions. Tamsulosin hydrochloride exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food: The time to maximum concentration (Tmax) is reached by 4-5 hours under fasting conditions and by 6-7 hours when tamsulosin hydrochloride capsules are administered with food.

Distribution: The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to 10 healthy male adults was 16 L, which is suggestive of distribution into the extracellular fluids in the body. Tamsulosin hydrochloride is extensively bound to human plasma proteins (94-99%), primarily alpha1-acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way in vitrostudies indicate that the binding of tamsulosin hydrochloride to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide or chlormadinone. Likewise, tamsulosin hydrochloride had no effect on the extent of binding of these drugs.

Metabolism: There is no enantiomeric bioconversion from tamsulosin hydrochloride to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolized by cytochrome (CY) P450 enzymes in the liver and less than 10% of the dose is excreted in the urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6 as well as via some minor participation of other CYP isoenzymes. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin hydrochloride and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5 alpha-reductase inhibitor for treatment of BPH). However, results of the in vitro testing of the tamsulosin hydrochloride interaction with diclofenac and warfarin were equivocal.

Excretion: On administration of the radiolabelled dose of tamsulosin hydrochloride to 4 healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to faeces (21%) over 168 hours. Because of absorption rate-controlled pharmacokinetics with tamsulosin hydrochloride modified-release capsules, the apparent half-life of tamsulosin hydrochloride is approximately 9-13 hours in healthy volunteers and 14-15 hours in the target population. Tamsulosin hydrochloride undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Pharmacokinetics in special populations:

Pediatric Use: Tamsulosin hydrochloride capsules are not indicated for use in paediatric populations.

Geriatric Use: Cross-study comparison of Tamsulosin hydrochloride capsules overall exposure (AUC) and half-life indicates that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in geriatric 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: The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate (30≤ CLcr 2) or moderate-severe (10≤ CLcr 2) renal impairment and 6 normal subjects (CLcr >90 mL/min/1.73 m2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with end-stage renal disease (CLcr <10 mL/min/1.73 m2) have not been studied.

Hepatic Impairment: The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic impairment (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 impairment do not require an adjustment in tamsulosin hydrochloride capsules dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic impairment.

Dutasteride

Absorption: Following administration of a single 0.5 mg dose of dutasteride, time to peak serum concentrations (Tmax) occurs within 2-3 hours. Absolute bioavailability in 5 healthy subjects is approximately 60% (range: 40% to 94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10-15%. This reduction is of no clinical significance.

Distribution: Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300-500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha1-acid glycoprotein (96.6%). In a study of healthy subjects (n = 26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/mL (range: 0.4 to 14 ng/mL) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months 11.5% of serum dutasteride concentrations partitioned into semen.

Metabolism: Dutasteride is extensively metabolized in humans. In vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride and the 6,4'-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4. In human serum following dosing to a steady state, unchanged dutasteride, three major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and two minor metabolites (6,4-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response have been detected. In vitro, the 4-hydroxydutasteride and 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of human 5 alpha-reductase. The activity of 6β-hydroxydutasteride is comparable to that of dutasteride.

Excretion: Dutasteride and its metabolites were excreted mainly in the faeces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range: 5% to 97%).The terminal elimination half-life of dutasteride is approximately 5 weeks at the steady state. The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4-6 months after discontinuation of treatment.

5.3 Preclinical safety data

Preclinical data reveals no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch BP

Hypromellose K 100 BP

Polysorbate 80 BP

Povidone K 30 BP

Purified Water BP

Isopropyl alcohol BP

Crospovidone BP

Magnesium Stearate BP

Colloidal anhydrous silica BP

Colorezy White 17F580001 IH

Colour Red oxide of Iron IH

Methylene Chloride BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months for the date of manufacturing.

6.4 Special precautions for storage

Store below 30º C. Protect from light. Keep out of reach of children

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

3X10 Tablets in Alu Alu blister pack

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/MANUFACTURER>

Stallion laboratories Pvt. Ltd.

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