Tamsulosin HCl + Finasteride

30XXXXX

Rx TamPlus®

200mcg / 5mg Sustained Release Capsule
400mcg / 5mg Sustained Release Capsule
Benign Prostatic Hypertrophy Drug Combination

FORMULATION

Each capsule contains:
Tamsulosin hydrochloride in
sustained release pellet 200mcg
Finasteride, USP in film coated tablet 5mg
Tamsulosin hydrochloride in
sustained release pellet 400mcg
Finasteride, USP in film coated tablet 5mg

DESCRIPTION

200mcg/ 5mg: Light blue (cap)/ light yellow (body) hard gelatin capsules of size "1" containing off-white to white colored pellets and a light blue colored circular biconvex film coated tablets.
400mcg/ 5mg: Light blue (cap)/ dark blue (body) hard gelatin capsules of size "1" containing off-white to white colored pellets and a light blue colored circular biconvex film coated tablets.

INDICATIONS

TAMSULOSIN PLUS FINASTERIDE is indicated for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH) in men with enlarged prostate to: improve symptoms, reduce the risk of acute urinary retention, reduce the risk of the need for surgery including transurethral resection of the prostate and prostatectomy, and reduce the risk of symptomatic progression of BPH.

CONTRAINDICATIONS

TAMSULOSIN PLUS FINASTERIDE is contraindicated in patients with a hypersensitivity to Tamsulosin hydrochloride or Finasteride, a history of orthostatic hypotension or severe hepatic insufficiency.

DOSAGE AND ADMINISTRATION

Adults: One capsule containing Tamsulosin hydrochloride (sustained release) 200mcg plus Finasteride 5mg once daily, 30 minutes after a meal. The dosage may be titrated upwards to one capsule containing Tamsulosin hydrochloride (sustained release) 400mcg plus Finasteride 5mg once daily, 30 minutes after a meal. Or as prescribed by the physician.

Elderly: One capsule containing Tamsulosin hydrochloride (sustained release) 200mcg plus Finasteride 5mg once daily, 30 minutes after a meal. The dosage may be titrated upwards to one capsule containing Tamsulosin hydrochloride (sustained release) 400mcg plus Finasteride 5mg once daily, 30 minutes after a meal. Or as prescribed by the physician.

Patients with Renal Impairment: In patients with mild to moderate renal impairment, start treatment with one capsule containing Tamsulosin hydrochloride (sustained release) 200mcg plus Finasteride 5mg once daily, 30 minutes after a meal. Caution should be exercised when using TAMSULOSIN PLUS FINASTERIDE in patients with severe renal impairment.

Patients with Hepatic Disease: In patients with mild to moderate hepatic impairment, start treatment with one capsule containing Tamsulosin hydrochloride (sustained release) 200mcg plus Finasteride 5mg once daily, 30 minutes after a meal. Use of TAMSULOSIN PLUS FINASTERIDE is contraindicated in patients with severe hepatic impairment.

PHARMACODYNAMICS

FINASTERIDE

The symptoms associated with Benign Prostatic Hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. The development and enlargement of the prostate gland is dependent on 5α-dihydrotestosterone (DHT), a potent androgen. Type II 5α-reductase metabolizes testosterone to DHT in the prostate. Finasteride is a competitive and specific inhibitor of Type II 5α-reductase with which it slowly forms a stable enzyme complex. Finasteride reduces serum DHT concentrations and produces a sustained regression in prostate volume of approximately 20% and a sustained increase in urinary flow rate.

TAMSULOSIN

The symptoms associated with Benign Prostatic Hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of α_1 adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. Tamsulosin, a α_1 adrenoceptor blocking agent, exhibits selectivity for α_1 receptors in the human prostate. At least three discrete α_1-adrenoceptor subtypes have been identified: α_1A, α_1B and α_1D; their distribution differs between human organs and tissue. Approximately 70% of the α_1-receptors in human prostate are of the α_1A subtype. Tamsulosin hydrochloride capsules are not intended for use as an antihypertensive drug.

PHARMACOKINETICS

FINASTERIDE

Absorption: In healthy young subjects, the mean bioavailability of Finasteride 5-mg tablets was 63% (range 34-108%). Maximum Finasteride plasma concentration averaged 37 ng/mL (range, 27-49 ng/mL) and was reached 1-2 hours post dose. Bioavailability of Finasteride was not affected by food.

Distribution: Mean steady-state volume of distribution was 76 liters (range, 44-96 liters). Approximately 90% of circulating Finasteride is bound to plasma proteins.

Metabolism: Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites possess no more than 20% of the 5α-reductase inhibitory activity of Finasteride.

Elimination: In healthy young subjects, the mean plasma clearance of Finasteride was 165 mL/min (range, 70-279 mL/min) and the mean elimination half-life in plasma was 6 hours (range, 3-16 hours). Following an oral dose of14C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces. The mean terminal half-life of Finasteride in subjects ⩾ 70 years of age was approximately 8 hours (range, 6-15 hours), compared with 6 hours (range, 4-12 hours; n=12) in subjects 45-60 years of age. As a result, mean AUC (0-24 hr) after 17 days of dosing was 15% higher in subjects ⩾70 years of age than in subjects 45-60 years of age.

Elderly: The elimination rate of Finasteride is decreased in the elderly (See Pharmacokinetics – Elimination); these findings however are of no clinical significance.

Patients with Renal Impairment: In patients with chronic renal impairment (ClCr 9.0 - 55 mL/min), AUC, maximum plasma concentration, half-life, and protein binding after a single dose of14C-finasteride was similar to values obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, Finasteride has been well tolerated in BPH patients with normal renal function receiving up to 80 mg/day for 12 weeks, where exposure of these patients to metabolites would presumably be much greater.

Patients with Hepatic Impairment: The effect of hepatic insufficiency on Finasteride pharmacokinetics has not been studied. Caution should be exercised when Finasteride is administered in patients with liver function abnormalities, as Finasteride is metabolized extensively in the liver.

TAMSULOSIN

Absorption: Absorption of Tamsulosin hydrochloride from 400mcg capsules 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. The time to maximum concentration (Tmax) is reached by four to five hours under fasting conditions and by six to seven hours when the dose is administered with food. Taking Tamsulosin capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (Cmax) compared to fed conditions. The effects of food on the pharmacokinetics of Tamsulosin hydrochloride are consistent regardless of whether it is taken with a light breakfast or a high-fat breakfast.

Distribution: The mean steady-state apparent volume of distribution of Tamsulosin hydrochloride after intravenous administration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body. Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way in vitro studies 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: Tamsulosin hydrochloride is extensively metabolized 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 metabolizing enzymes may lead to increased exposure to Tamsulosin. The metabolites of Tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate 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 (5alpha-reductase inhibitor for treatment of BPH). However, results of the in vitro testing of the Tamsulosin hydrochloride interaction with diclofenac and warfarin were equivocal.

Elimination: On administration of a radio labeled dose of Tamsulosin hydrochloride to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours.
Following intravenous or oral administration of an immediate-release formulation of Tamsulosin, the elimination half-life of Tamsulosin hydrochloride in plasma ranged from five to seven hours. The apparent half-life of tamsulosin hydrochloride in this modified release formulation is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population. Tamsulosin hydrochloride undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Elderly: Cross-study comparison of AUC and half-life indicate 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.

Patients with Renal Impairment: 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 dosage. However, patients with end stage renal disease (ClCr <10 mL/min/1.73m2) have not been studied.

Patients with Hepatic Impairment: The pharmacokinetics of Tamsulosin hydrochloride has 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 dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Before therapy with TAMSULOSIN PLUS FINASTERIDE is initiated the patient should be examined in order to exclude the presence of other conditions such as carcinoma of the prostate which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with TAMSULOSIN PLUS FINASTERIDE and periodically thereafter.

FINASTERIDE
No clinical benefit has yet been demonstrated in patients with prostate cancer treated with finasteride. Generally, when PSA assays are performed a baseline PSA>10 ng/ml prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with finasteride. A baseline PSA <4 ng/ml does not exclude prostate cancer. Finasteride causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with Finasteride should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. In patients treated with Finasteride for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer. Any sustained increase in PSA levels of patients treated with Finasteride should be carefully evaluated, including consideration of non-compliance to therapy with Finasteride. Percent free PSA (free to total PSA ratio) is not significantly decreased by Finasteride and remains constant even under the influence of Finasteride. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment is necessary.

TAMSULOSIN
As with other α blockers, a reduction in blood pressure can occur in individual cases during treatment with Tamsulosin, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness) the patient should sit or lie down until the symptoms have disappeared. The treatment of severely renally impaired patients (creatinine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied. The '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 TAMSULOSIN PLUS FINASTERIDE in patients for whom cataract surgery is scheduled is not recommended. Discontinuing TAMSULOSIN PLUS FINASTERIDE 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of cessation of therapy prior to cataract surgery has not yet been established. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with TAMSULOSIN PLUS FINASTERIDE in order to ensure that appropriate measures will be in place to manage IFIS during surgery should it occur.

DRUG INTERACTIONS
FINASTERIDE
No clinically important drug interactions have been identified. Finasteride does not appear to significantly affect the cytochrome P450 -linked drug metabolizing enzyme system. Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found. Although specific interaction studies were not performed in clinical studies, Finasteride was used concomitantly with ACE inhibitors, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H2 antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

TAMSULOSIN
No clinically significant effects on blood pressure or pulse rate were observed when tamsulosin was given concomitantly with atenolol, enalapril, nifedipine or theophylline. Concomitant administration of cimetidine increases plasma levels of tamsulosin. Concomitant administration of furosemide reduces plasma levels of Tamsulosin. Plasma levels of tamsulosin however remain within the normal range when used together with furosemide or cimetidine. In vitro, neither diazepam, propranolol, trichlormethiazide, chlormadinon, amitryptyline, diclofenac, glibenclamide, simvastatin nor warfarin changes 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 observed during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolizing enzyme system), involving amitriptyline, salbutamol, glibenclamide and Finasteride. Diclofenac and warfarin, however, may increase the elimination rate of Tamsulosin. There is a theoretical risk of enhanced hypotensive effect when given concurrently with drugs which may reduce blood pressure, including anesthetic agents and other α-adrenoceptor antagonists.

ADVERSE EFFECTS
FINASTERIDE
In controlled clinical studies where patients received 5 mg of Finasteride over periods of up to four years, the following adverse reactions were considered possibly, probably or definitely drug-related and occurred with a frequency greater than placebo and greater than or equal to 1%: impotence, decreased libido, ejaculation disorder, decreased volume of ejaculate; breast enlargement, breast tenderness and rash. There was no evidence of increased adverse experiences with increased duration of treatment with Finasteride and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment. The MTOPS study compared Finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of Finasteride 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder events without regard to drug relationship were: Finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%. The following additional adverse experiences have been reported in post-marketing experience: hypersensitivity reactions, including pruritus, urticaria and swelling of the lips and face; testicular pain.

TAMSULOSIN
The following adverse reactions have been reported with the use of Tamsulosin: dizziness, abnormal ejaculation and, less frequently (1-2%) headache, asthenia, postural hypotension, palpitations and rhinitis. Gastrointestinal reactions such as nausea, vomiting, diarrhea, and constipation can occasionally occur. Hypersensitivity reactions such as rash, pruritus, and urticaria can occur occasionally. As with other alpha-blockers, drowsiness, blurred vision, dry mouth or edema can occur. Syncope has been reported rarely, and there have been very rare reports of angioedema and priapism. During cataract surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of Tamsulosin during post-marketing surveillance.

USE IN PREGNANCY AND LACTATION
Not applicable. TAMSULOSIN PLUS FINASTERIDE is indicated for male patients only.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without a prescription.

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA : www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORE AT TEMPERATURES NOT EXCEEDING 30°C

AVAILABILITY
Tamsulosin HCl + Finasteride (TamPlus®) 200mcg / 5mg Sustained Release Capsule X 30 Capsules / box in alu-alu blister pack.
Tamsulosin HCl + Finasteride (TamPlus®) 400mcg / 5mg Sustained Release Capsule X 30 Capsules / box in alu-alu blister pack.

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REGISTRATION NUMBER
200mcg/5mg: DR-XY38889
400mcg/5mg: DR-XY38883

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