Tamsolin® Plus

[Tamsulosin HCl + Dutasteride]

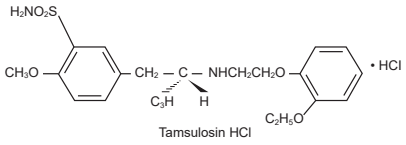
ٹیمسولن پلس

Capsules 0.4mg+0.5mg

DESCRIPTION

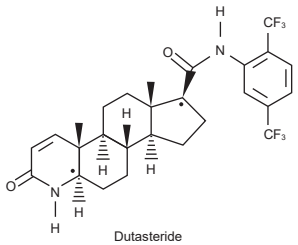
Tamsolin Plus contains tamsulosin HCl (an antagonist of alpha1A-adrenoceptors in the prostate) and dutasteride (a selective inhibitor of both, type 1 and type 2 isoforms of steroid 5 alpha-reductase).

Tamsulosin HCl is a synthetic compound chemically designated as (-)-(R)-5-[2-[[2-(o-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. The molecular formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S$•HCl and the structural formula is:



Tamsulosin HCl

Dutasteride is a synthetic 4-azasteroid compound chemically designated as (5α,17 β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The molecular formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$ and the structural formula is:



Dutasteride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamsolin Plus (Tamsulosin HCl + Dutasteride) Capsules are available for oral administration as:

Tamsolin Plus Capsules 0.4mg + 0.5mg
Each capsule contains:
Tamsulosin HCl…0.4mg
(as modified release pellets)
Dutasteride…0.5mg
(as soft gel capsule)

CLINICAL PHARMACOLOGY

Mechanism of Action

Tamsulosin HCl inhibits α_{1a} and α_{1d} adrenergic receptors in the stromal prostatic smooth muscle 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.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2, 5 alpha-reductase isoenzymes, with which it forms a stable enzyme complex. Dutasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5 alpha-reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Pharmacokinetics

Absorbtion

Tamsulosin HCl is absorbed from the intestine and is almost completely bioavailable. Following oral administration of a single 0.5mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60%.

Effect of Food

Both the rate and extent of absorption of tamsulosin HCl are reduced when taken within 30 minutes of a meal. Uniformity of absorption can be promoted by the patient always taking Tamsulosin HCl + Dutasteride after the same meal. Tamsulosin HCl shows dose proportional plasma exposure. The bioavailability of dutasteride is not affected by food.

Distribution

In man tamsulosin HCl is about 99% bound to plasma proteins. The volume of distribution is small (about 0.2l/kg).

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (>99.5%). Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months. Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Metabolism

There is no enantiomeric bioconversion from tamsulosin HCl [R(-) isomer] to the S(+) isomer in humans. Tamsulosin HCl is extensively metabolised by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. Inhibition of hepatic drug metabolising enzymes may lead to increased exposure to tamsulosin HCl. The metabolites of tamsulosin HCl undergo extensive conjugation to glucuronide or sulfate prior to renal excretion. Dutasteride is extensively metabolised in humans. Following oral dosing of dutasteride 0.5mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged dutasteride in the feces. The remainder is excreted in the feces 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.

Elimination

Tamsulosin HCl 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 HCl in plasma range from 5 to 7 hours. Due to the absorption rate-controlled pharmacokinetics with tamsulosin HCl modified release capsules, the apparent elimination half-life of tamsulosin HCl in the fed state is approximately 10 hours and in the steady state in patients approximately 13 hours.

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 3mg/mL), dutasteride is cleared rapidly by both the concentration dependent and concentration independent elimination pathways. Single doses of 5mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 days. At therapeutic concentrations, following repeat dosing of 0.5mg/day, the slower, linear elimination pathway is dominating and the half-life is approx. 3-5 weeks.

Special population

Patients with renal impairment

Patients with renal impairment do not require an adjustment in tamsulosin HCl capsules dosing. However, patients with endstage renal disease (CL_{cr} < 10 mL/min/1.73m^2) have not been studied.

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5mg 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.

Patients with hepatic impairment

Patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin HCl dosage. Tamsulosin HCl has not been studied in patients with severe hepatic dysfunction. 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.

THERAPEUTIC INDICATIONS

Tamsolin Plus (Tamsulosin HCl + Dutasteride) treats and prevents progression of benign prostatic hyperplasia (BPH) through alleviating symptoms, reducing prostate size (volume), improving urinary flow rate and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery.

DOSAGE AND ADMINISTRATION

Do not chew. Swallow the capsule whole.
For use by men only.

Adults (including elderly)

The recommended dose of Tamsolin Plus (Tamsulosin HCl + Dutasteride) is one capsule (0.4mg + 0.5mg) taken once daily approximately 30 minutes after the same meal each day.

Where appropriate, Tamsolin Plus (Tamsulosin HCl + Dutasteride) may be used to substitute concomitant dutasteride and tamsulosin HCl in existing dual therapy to simplify treatment.

Where clinically appropriate, direct change from dutasteride or tamsulosin HCl monotherapy to Tamsolin Plus (Tamsulosin HCl + Dutasteride) may be considered.

Special population

Patients with renal impairment

No adjustment in dosage is anticipated for patients with renal impairment.

Patients with hepatic impairment

Caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of Tamsolin Plus (Tamsulosin HCl + Dutasteride) is contraindicated.

Pediatric population

Tamsolin Plus (Tamsulosin HCl + Dutasteride) is contraindicated in the pediatric population (under 18 years of age).

CONTRAINDICATIONS

Tamsulosin HCl + Dutasteride is contraindicated in:

- Patients with known hypersensitivity to dutasteride, tamsulosin HCl (including tamsulosin induced angio-edema), soya, peanut or to any excipient of the product.
- Women, children and adolescents.
- Patients with a history of orthostatic hypotension.
- Patients with severe hepatic impairment.

ADVERSE REACTIONS

Common

Dizziness, Impotence, Altered (decreased) libido, Ejaculation disorders and Breast disorders.

Uncommon

Cardiac failure.

PRECAUTIONS

General

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

Men taking Tamsulosin HCl + Dutasteride should be regularly evaluated for prostate cancer.

Prostate specific antigen (PSA)

Tamsulosin HCl + Dutasteride causes a decrease in mean serum PSA (prostate-specific antigen) levels by approximately 50%, after 6 months of treatment. Patients receiving Tamsulosin HCl + Dutasteride should have a new PSA baseline established after 6 months of treatment with Tamsulosin HCl + Dutasteride. 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 Tamsulosin HCl + Dutasteride and periodically thereafter.

Breast neoplasia

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.

Hypotension

- *Orthostatic:* As with other alpha1- adrenoceptor antagonists, a reduction in blood pressure can occur during treatment with tamsulosin HCl, as a result of which, rarely, syncope can occur. Patients beginning treatment with Tamsulosin HCl + Dutasteride 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 minimize the potential for developing postural hypotension the patient should be hemodynamically stable on an alpha1- adrenoceptor antagonist prior to initiating use of phosphodiesterase-5 inhibitors.
- *Symptomatic:* Caution is advised when alpha adrenergic blocking agents including tamsulosin HCl are co-administered with phosphodiesterase-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil). Alpha1- adrenoceptor antagonists and phosphodiesterase-5 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 HCl. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with Tamsulosin HCl + Dutasteride 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 Tamsulosin HCl + Dutasteride in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Discontinuing tamsulosin HCl 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 HCl with strong inhibitors of CYP3A4 (e.g. ketoconazole) or to a lesser extent, with strong inhibitors of CYP2D6 (e.g. paroxetine) can increase tamsulosin HCl exposure.

Tamsulosin HCl 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 metabolizers of CYP2D6.

Hepatic impairment

Tamsulosin HCl + Dutasteride has not been studied in patients with liver disease. Caution should be used in the administration of Tamsulosin HCl + Dutasteride to patients with mild to moderate hepatic impairment.

Blood Donation

Patients should not donate blood until 6 months after their last dose of Tamsulosin HCl + Dutasteride. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Priapism

Priapism (persistent painful penile erection unrelated to sexual activity) has been associated with the use of alpha-adrenergic antagonists, including tamsulosin HCl. Because this condition can lead to permanent impotence if not properly treated, patients should be advised about the seriousness of the condition.

Sulfa Allergy

In patients with sulfa allergy, allergic reaction to tamsulosin HCl has been rarely reported. If a patient reports a serious or life-threatening sulfa allergy, caution is warranted when administering tamsulosin HCl-containing products.

Effects on ability to drive and use machines

Patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Tamsulosin HCl + Dutasteride.

Pregnancy

The use of Tamsulosin HCl + Dutasteride is contraindicated in women of childbearing potential and during pregnancy.

Nursing Mothers

Tamsulosin HCl + Dutasteride is contraindicated for use in women of childbearing potential, including nursing women. It is not known whether dutasteride or tamsulosin HCl is excreted in human milk.

DRUG INTERACTION

Strong Inhibitors of CYP3A4

Tamsulosin HCl + Dutasteride should not be coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) as this can significantly increase tamsulosin HCl and dutasteride exposure.

Inhibitors of CYP2D6 and Moderate Inhibitors of CYP3A4

Tamsulosin HCl-containing products should be used with caution when co-administered with moderate inhibitors of CYP3A4 (e.g., erythromycin), strong (e.g., paroxetine) or moderate (e.g., terbinafine) inhibitors of CYP2D6 or in patients known to be poor metabolizers of CYP2D6, as there is a potential for significant increase in tamsulosin HCl exposure.

Cimetidine

Caution is advised when tamsulosin HCl-containing products are co-administered with cimetidine.

Other Alpha Adrenergic Antagonists

Tamsulosin HCl-containing products should not be coadministered with other alpha adrenergic antagonists because of the increased risk of symptomatic hypotension.

Phosphodiesterase-5 Inhibitors (PDE-5 Inhibitors)

Caution is advised when tamsulosin HCl-containing products are co-administered with phosphodiesterase-5 inhibitors. Alpha adrenergic antagonists and phosphodiesterase-5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these 2 drug classes can potentially cause symptomatic hypotension.

Warfarin

Caution should be exercised with concomitant administration of warfarin and tamsulosin HCl-containing products.

OVERDOSAGE

Tamsulosin HCl

Should overdosage of tamsulosin HCl lead to 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 then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin HCl is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit. 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.

Dutasteride

There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride into consideration.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Tamsolin Plus (Tamsulosin HCl + Dutasteride) Capsules 0.4mg+0.5mg are available in pack of 10 capsules.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com

29-30/27, K.I.A., Karachi, Pakistan

L-200010703