

Dutasteride+Tamsulosin Hydrochloride

Amso-D

500 mcg/400 mcg Capsule
Alpha-Adrenoceptor Antagonist



PRODUCT DESCRIPTION

Dutasteride and Tamsulosin Hydrochloride Capsules 500 mcg & 400 mcg is size "1" hard gelatin capsule orange opaque/ brown opaque color filled with white to off white color coated pellets.

Dutasteride and Tamsulosin Hydrochloride Capsules 500 mcg & 400 mcg are packed in 3 x 10 Alu-Alu blister and 6 x 10 Alu-Alu blister.

FORMULATION/COMPOSITION

Each capsule contains: Dutasteride 500 mcg Tamsulosin Hydrochloride 400 mcg

Pharmacodynamics and Pharmacokinetics

Mechanism of action:

Dutasteride inhibits both type 1 and type 2, 5- α 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 $\alpha 1a$ and $\alpha 1d$ adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the $\alpha 1$ -receptors in the prostate are of the $\alpha 1a$ subtype.

Pharmacodynamics:

Dutasteride-tamsulosin is a combination of two drugs: Dutasteride, a dual 5 α -reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of $\alpha 1a$ and $\alpha 1d$ adrenoceptor. 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.

Pharmacokinetics

Absorption:

Dutasteride

The bioavailability of Dutasteride is approximately 60% and peak serum concentration is achieved after 2 to 3 hours. The time to steady state is dose dependent, and at a dose of 0.5 mg/day is approximately 3 months.

Tamsulosin

Under fasting conditions absorption of the orally administered recommended dosage of tamsulosin is greater than 90%. The time to maximum concentration is 4 to 5 hours under fasting condition and 6 to 7 hours when tamsulosin is administered with food. Administration of tamsulosin under fasting conditions results in a 40% to 70% increase in peak concentrations compared to the same dosage administered with food. The time to steady state is approximately 5 days.

Tamsulosin is absorbed from the gastrointestinal tract; 90% following oral administration. The extent and rate of absorption is reduced in the presence of food.

Distribution:

Dutasteride

More than 99.5% of circulating Dutasteride is bound to plasma proteins, and has a volume of distribution of 300 to 500 L. Moreover, extensive distribution of drug observed, with a steady state volume of distribution of 300 -500 L. Plasma concentrations may be reduced by 10 - 15% with concurrent food administration, though this has not been shown to be clinically significant.

It is highly protein bound (>99%), mainly to albumin and α -1 acid glycoprotein.

Tamsulosin

More than 94% of tamsulosin is bound to circulating plasma proteins and the drug has a volume of distribution of 16 L. 8L is distributed into extracellular fluid in the body.

More than 94% binding to plasma proteins.

Metabolism:

Dutasteride

Dutasteride is extensively metabolized in vivo. In vitro, dutasteride is metabolized by the cytochrome P450 3A4 and 3A5 to 3 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 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.

Tamsulosin

There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. 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.

Elimination:

Dutasteride

Clearance is linear at 0.58 L/hour, resulting in a half-life of up to 5 weeks.

Tamsulosin

Tamsulosin undergoes restrictive clearance with a systemic clearance of 2.88 L/hour and a half-life of 9 to 15 hours.

Paediatric Patients:

Benign prostatic hyperplasia is not a disease of childhood. Dutasteride - tamsulosin is contraindicated for use in pediatric patients. Safety and effectiveness in pediatric patients have to be established.

Hepatically-Impaired Patients:**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

Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

INDICATION:

Dutasteride and Tamsulosin is indicated for the treatment of the following:

- 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.

DOSAGE AND ROUTE OF ADMINISTRATION

The recommended dosage of dutasteride and tamsulosin hydrochloride capsules is 1 capsule (500 mcg dutasteride and 400 mcg tamsulosin hydrochloride) taken once daily approximately 30 minutes after the same meal each day. Patients should be advised that AMSO-D should not be taken on an empty stomach as this may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

Route of Administration: Oral

CONTRAINDICATION, PRECAUTION & WARNING**Contraindications:**

AMSO-D is contraindicated in patients with known hypersensitivity to dutasteride, other 5 α -reductase inhibitors, tamsulosin hydrochloride or any component of the preparation. women and children (see Section FERTILITY, PREGNANCY AND LACTATION). patients with a history of orthostatic hypotension patients with severe hepatic impairment (child-Pugh scores >9). patients with severe renal impairment (creatinine clearance less than 10 mL/min). combination with another α 1-adrenergic blocker.

- AMSO-D is contraindicated in:
- Women and children and adolescents.
- Patients with hypersensitivity to dutasteride, other 5-*alpha reductase* inhibitors, tamsulosin (including tamsulosin induced angioedema), soya, peanut (soya lecithin)
- Patients with a history of orthostatic hypotension.
- Patients with severe hepatic impairment

Warnings and special precautions:

Combination therapy should be prescribed after careful benefit risk assessment due to the potential increased risk of adverse events (including cardiac failure).

AMSO-D should be prescribed after careful benefit risk assessment and after consideration of alternative treatment options including monotherapies. AMSO-D must be taken approximately 30 minutes after the same meal each day (see Section DOSE AND METHOD OF ADMINISTRATION). Taking AMSO-D on an empty stomach may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

Blood Donation

Men being treated with any dutasteride-containing products, including AMSO-D should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients treated with α 1-adrenergic blockers, including tamsulosin. This syndrome is characterized by the combination of a flaccid iris that billows as a result of intra-operative irrigation currents, prolapse of the iris toward the phacoemulsification incisions, and progressive intra-operative miosis despite pre-operative dilation with standard mydriatic drugs. IFIS may increase the risk of eye complications during and after operation. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with AMSO-D in order to ensure that appropriate measures will be in place to manage IFIS if it occurs during surgery. Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping of therapy prior to cataract surgery has not yet been established.

Leaking capsules Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water (see Section FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy and Use in lactation).

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 (see Section INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 (e.g. erythromycin), a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6 (see Section INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Sulfur allergy A causal relationship between tamsulosin and sulfur allergy has not been established, however there is a theoretical risk of an allergic reaction when tamsulosin is taken by patients with a history of sulfur allergy. If a patient reports a serious or life threatening sulphur allergy, caution is warranted when administering AMSO-D.

Use in hepatic impairment The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease (see Section DOSE AND METHOD OF ADMINISTRATION and Section PHARMACOKINETIC PROPERTIES). AMSO-D is contraindicated in patients with severe hepatic impairment. Use in renal impairment Severe renal impairment, with creatinine clearance of less than 10 mL/min, is a CONTRAINDICATION, as these patients have not been studied.

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Use in renal impairment Severe renal impairment, with creatinine clearance of less than 10 mL/min, is a CONTRAINDICATION, as these patients have not been studied.

Use in the elderly See Section SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pediatric use The use of dutasteride/tamsulosin hydrochloride is contraindicated in children. Dutasteride/ tamsulosin hydrochloride has not been studied in children.

Effects on laboratory tests No data available

DRUG INTERACTIONS

Dutasteride is metabolized by the human cytochrome P-450 isoenzyme CYP3A4. There have been no drug interaction studies for AMSO-D. The following statements reflect the information available on the individual components. Interactions of dutasteride and tamsulosin with cytochrome P450 Inhibitors .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 α -reductase at 6 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.

ADVERSE DRUG REACTIONS

Common side effects These may affect up to 1 in 10 men taking Dutasteride and Tamsulosin HCl Capsules 500 mcg & 400 mcg

- Decreased sex drive (libido)
- Difficulty with ejaculation, such as a decrease in the amount of semen released during sex
- Breast enlargement or tenderness (gynecomastia)
- Dizziness.

Uncommon side effects

- Heart failure (heart becomes less efficient at pumping blood around the body. You may have symptoms such as shortness of breath, extreme tiredness and swelling in your ankles and legs)
- Low Blood pressure on standing
- Fast heartbeat (palpitations)
- Constipation, diarrhoea, vomiting, feeling sick (nausea)
- Weakness or loss of strength Headache Itchy, blocked or runny nose (rhinitis) Skin rash, hives, itching. Hair loss (usually from the body) or hair growth.

Rare side effects These may affect up to 1 in 1,000 men

- Swelling of the eyelids, face, lips, arms
- Fainting

Very rare side effects These may affect up to 1 in 10,000 men

- Persistent painful erection of the penis (priapism)
- Serious skin reactions (Stevens-Johnson syndrome).

Other side effects Other side effects have occurred in a small number of men, but their exact frequency is not known (the frequency cannot be estimated from available data):

- abnormal or fast heartbeat (arrhythmia or tachycardia or atrial fibrillation)
- shortness of breath (dyspnoea)
- depression pain and swelling in testicles
- nose bleeds
- severe skin rash
- changes in vision (blurred vision or visual impairment)
- dry mouth

OVERDOSE & TREATMENT

Dutasteride

In studies of healthy volunteers, 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 cases of suspected overdosage, symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride in consideration.

Tamsulosin

In case of acute hypotension occurring after overdosage with tamsulosin, 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 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 is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit in removing tamsulosin from the body. Acute overdose with 5 mg tamsulosin has been reported. Acute hypotension (systolic blood pressure 70 mmHg), vomiting and diarrhea were observed, which were treated with fluid replacement and the patient was discharged the same day. One patient reported an overdose of 30 x 0.4 mg tamsulosin capsules. Following ingestion, the patient reported a headache judged to be severe and probably drug-related that resolved the same day.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

DOSAGE FORM & PACKAGING AVAILABLE

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INSTRUCTION AND SPECIAL PRECAUTION FOR HANDLING AND DISPOSAL

Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the carton.

The expiry date refers to the last day of that month. Store at room temperature below 30°C, Keep out of the reach of children. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

IMPORTED AND DISTRIBUTED BY:



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AVAILABILITY

Dutasteride+Tamsulosin (AMSO-D) 500 mcg/400 mcg Capsule: 30 capsules in 100 mL HDPE bottle in a box.

CAUTION

Food, Drug, Device, and Cosmetic Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

For suspected drug reaction/s, report to www.fda.gov.ph and email to pv@biocarelifesciences.com

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