TAMSULOSIN HYDROCHLORIDE 0.4 mg CAPSULES

tamsulosin hydrochloride

Presentation

Capsule 0.4 mg: a capsule (size #2) with an orange body, brown cap and imprinted with ‘R’ on cap and ‘TSN400’ on body in black edible ink.

Each capsule contains 0.4 mg tamsulosin hydrochloride equivalent to 0.367 mg tamsulosin, which can be identified as white to off-white granular beads.

Uses

Actions

Tamsulosin hydrochloride binds selectively and competitively to postsynaptic α1-adrenoceptors, particularly to subtypes alpha1A and alpha1D. It brings about relaxation of prostatic and urethral smooth muscle.

Tamsulosin Hydrochloride 0.4 mg increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra.

It also improves the irritative symptoms in which bladder instability plays an important role.

These effects on storage and voiding symptoms are maintained during long-term therapy. The need for surgical treatment is significantly delayed.

Alpha1-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Tamsulosin Hydrochloride MR 0.4 mg.

Pharmacokinetics

Absorption

Tamsulosin is rapidly absorbed from the intestine and is almost completely bioavailable. Absorption of tamsulosin is reduced by a recent meal.

The patient always taking TAMSULOSIN HYDROCHLORIDE 0.4 mg capsules after the same meal can promote uniformity of absorption.

Tamsulosin shows linear kinetics.

After a single dose of TAMSULOSIN HYDROCHLORIDE 0.4 mg capsules in the fed state, plasma levels of tamsulosin peak at around 6 hours and in the steady state, which is reached by day 5 of multiple dosing, Cmax in patients is about two-thirds higher than that reached after a single dose. Although this was seen in elderly patients, the same finding would also be expected in young ones.

There is a considerable inter-patient variation in plasma levels both after single and multiple dosing.
Distribution

In humans tamsulosin is about 99% bound to plasma proteins and the volume of distribution is small (about 0.2 L/kg).

Biotransformation

Tamsulosin capsules contain tamsulosin as the R(-) isomer. In humans, there is no in vivo conversion to the less active S(+) isomer. Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged drug. Tamsulosin is metabolised in the liver. In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin metabolism by other CYP isozymes. Inhibition of hepatic drug metabolising enzymes may lead to increased exposure to tamsulosin (see Interactions with other medicines). In rats, tamsulosin was seen to cause minimal induction of microsomal liver enzymes. No dose adjustment is warranted in hepatic insufficiency (see also Contraindications).

None of the metabolites is more active than the original precursor compound.

Excretion

Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present in the form of unchanged medicine.

After a single dose of TAMSULOSIN HYDROCHLORIDE in the fed state, and in the steady state in patients, elimination half-lives of about 10 and 13 hours respectively have been measured.

The presence of renal impairment does not warrant lowering the dose.

Indications

Treatment of functional symptoms of benign prostatic hyperplasia (BPH).

Dosage and Administration

One capsule daily, to be taken after breakfast, or the first meal of the day.

The capsule should be swallowed whole and should not be crushed or chewed, as this will interfere with the modified release of the active ingredient.

Contraindications

Hypersensitivity to tamsulosin hydrochloride or any other component of the product.

A history of orthostatic hypotension.

Severe hepatic insufficiency (Child-Pugh scores >9).

Severe renal impairment with creatinine clearance of less than 10 mL/min.

Concurrent use of another α₁-adrenoceptor inhibitor.
Warning and Precautions

Syncope and Postural hypotension

Patients beginning treatment with TAMSULOSIN HYDROCHLORIDE capsules should be cautioned to avoid situations where injury could result should syncope occur. Postural hypotension can occur during treatment with TAMSULOSIN HYDROCHLORIDE capsules, but rarely results in syncope. However, the patient should be warned of this possibility and advised to sit or lie down if symptoms of hypotension should occur.

Exclusion of prostatic carcinoma and other urological conditions

Carcinoma of the prostate and other conditions which can cause the same symptoms as benign prostatic hyperplasia should be excluded before starting therapy with TAMSULOSIN HYDROCHLORIDE capsules. Digital rectal examination and, as considered appropriate, determination of prostate specific antigen should be performed before treatment and at regular intervals afterwards.

Myocardial ischaemia

Patients with myocardial infarction or angina pectoris within the preceding six months were excluded from the Phase III clinical studies. As a result, the safety of TAMSULOSIN HYDROCHLORIDE capsules in these patients has not been formally assessed.

Dizziness

As TAMSULOSIN HYDROCHLORIDE capsules may cause dizziness, patients should be warned to take care whilst operating machinery or driving.

Intra-operative Floppy Iris Syndrome

Intra-operative Floppy Iris Syndrome' (IFIS) has been observed during cataract surgery in some patients taking or who have previously been treated with α1-adrenoceptor antagonists. This variant of small pupil syndrome is characterised by the combination of a flaccid iris that billows in response to intra-operative irrigation currents, progressive intra-operative miosis despite pre-operative dilation with standard mydriatic medicines, and potential prolapse of the iris toward the phaco-emulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilisation of iris hooks, iris dilator rings, or visco-elastic substances. There does not appear to be a benefit of stopping α1-adrenoceptor antagonist therapy prior to cataract surgery.

Carcinogenicity/mutagenicity/ impaired fertility

Reproduction toxicity in rats, carcinogenicity in mice and rats and in vivo genotoxicity have been conducted.

Oral (dietary) administration of tamsulosin for up to 2 years in rats and mice was associated with an increased incidence of pituitary adenoma, mammary gland hyperplasia, mammary gland fibroadenoma and (in mice only) mammary gland adenocarcinoma. These effects occurred at plasma tamsulosin concentrations (AUC) up to 10 times lower than those expected in men undergoing treatment with TAMSULOSIN HYDROCHLORIDE capsules, but they were observed only in female animals and are probably due to the hyperprolactinaemic effect of tamsulosin. It is not known if TAMSULOSIN HYDROCHLORIDE capsules elevates prolactin during prolonged administration in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in female rodents is unknown.

Tamsulosin produced no evidence of genotoxic potential in assays for gene mutation (Ames reverse mutation test and mouse lymphoma thymidine kinase assay), chromosomal damage
Chinese hamster ovary cells and mouse micronucleus assay) and other genotoxic effects (unscheduled DNA repair synthesis and in vivo sister chromatid exchange).

α-adrenoceptor antagonists are known to reduce male fertility by affecting penile erection, emission and/or ejaculation. In male rats, a severe reduction in male copulation rate and fertility was observed after a single dose or after repeated oral doses of tamsulosin. Spermatogenesis was not affected in the rat studies, and the effect on fertility was reversible. The no effect dose on male rat fertility was associated with plasma tamsulosin levels (AUC) at least 50% of those expected in human males treated with TAMSULOSIN HYDROCHLORIDE capsules.

Treatment of female rats with tamsulosin caused disruption of the oestrus cycle and a severe reduction in fertility, due to interference of fertilisation with the ova. These effects were shown to be reversible.

Inhibitors of Cytochrome P450 CYP3A4

Tamsulosin should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (see Interactions).

Use in pregnancy (Category B2)

TAMSULOSIN HYDROCHLORIDE capsules are intended for use only in males.

Tamsulosin, at oral doses causing maternal toxicity, was not embryotoxic or teratogenic when administered during gestation in rats (doses up to 300 mg/kg/day) or rabbits (doses up to 50 mg/kg/day). However, administration of tamsulosin during the peri-/post-natal period was associated with a higher incidence of stillbirths and reduced pup weight gain after birth. No adverse effects on development or reproductive performance were observed on surviving pups, however, there is some evidence for impairment of offspring reproductive capacity when maternal treatment with tamsulosin is started before pregnancy.

Use in lactation

TAMSULOSIN HYDROCHLORIDE capsules are intended for use only in males.

In female rats, tamsulosin and/or its metabolites were shown to pass into milk after oral administration of the medicine during lactation. The effect on the newborn is not known.

Other populations

TAMSULOSIN HYDROCHLORIDE capsules are not indicated for use in women or children.

Renal impairment

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

Hepatic impairment

In a study of patients with moderate hepatic impairment, free tamsulosin levels remained unchanged after treatment with 400 µg tamsulosin hydrochloride capsules when compared to normal subjects. Therefore no dose adjustment for TAMSULOSIN HYDROCHLORIDE capsules is expected in patients with mild to moderate hepatic impairment.

Severe hepatic impairment (Child-Pugh scores >9) is a CONTRAINDICATION.
Adverse Reactions

Priapism

Rarely, tamsulosin, like other alpha-1 antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction.

Abnormal ejaculation

Patients should be advised on the potential for abnormal ejaculation to occur upon commencement of TAMSULOSIN HYDROCHLORIDE capsule treatment. Retrograde ejaculation is the most commonly reported abnormal ejaculation event associated with the use of TAMSULOSIN HYDROCHLORIDE capsules (see Table 1).

Clinical trials

Table 1 shows the incidence of undesirable effects following 400 µg TAMSULOSIN HYDROCHLORIDE treatment. This data is based on a phase 3 clinical study in which there were no relevant differences between the treatment and placebo groups in the percentage of patients reporting at least 1 Treatment Emergent Adverse Event (TEAE). Most TEAEs were of mild or moderate intensity.

The most frequent TEAEs were ejaculation disorders. These are TEAEs that are often associated with α1-AR antagonists.

Table 1: Adverse events associated with TAMSULOSIN HYDROCHLORIDE in a placebo-controlled study.

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=356</th>
<th>TAMSULOSIN HYDROCHLORIDE CAPSULES N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiovascular class effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>1 (0.3%)</td>
<td>6 (1.7%)</td>
</tr>
<tr>
<td>Ejaculation failure</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Semen volume reduced</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Ejaculation delayed</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Ejaculation disorder NOS</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Abnormal ejaculation pooled</td>
<td>1 (0.3%)</td>
<td>7 (1.9%)</td>
</tr>
<tr>
<td>Headache NOS</td>
<td>4 (1.1%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Rhinitis NOS</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>SUB-TOTAL</strong></td>
<td>7 (2.0%)</td>
<td>16 (4.4%)</td>
</tr>
</tbody>
</table>

Cardiovascular class effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=356</th>
<th>TAMSULOSIN HYDROCHLORIDE CAPSULES N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>5 (1.4%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Dizziness aggravated</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Placebo N=356</td>
<td>TAMSULOSIN HYDROCHLORIDE CAPSULES N=360</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Dizzy spell</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dizziness pooled</td>
<td>5 (1.4%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2 (0.6%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Tachycardia NOS</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Hypotension NOS</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Orthostatic/circulatory collapse</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Depressed level of/loss of consciousness</td>
<td>0 (0.0%)</td>
<td>1 (0.03%)</td>
</tr>
<tr>
<td><strong>SUB-TOTAL</strong></td>
<td><strong>8 (2.2%)</strong></td>
<td><strong>9 (2.5%)</strong></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>13 (3.7%)</strong></td>
<td><strong>25 (6.9%)</strong></td>
</tr>
</tbody>
</table>

NOS = Not Otherwise Specified.

A patient may experience a TEAE more than once or may experience more than one TEAE within the same System Organ Class.

The following treatment-related adverse events were reported from clinical trials, where Common is ≥ 1% and <10%; Uncommon is ≥ 0.1% and <1%; Rare is ≥ 0.01% and <0.1%; and Very rare is <0.01%.

**Cardiac disorders**

Uncommon: palpitations.

**Gastro-intestinal disorders**

Uncommon: constipation, diarrhoea, nausea, vomiting, dry mouth.

**General disorders**

Uncommon: asthenia.

**Nervous system disorders**

Common: dizziness (1.3%).

Uncommon: headache.

Rare: syncope.

**Reproductive system disorders**

Uncommon: abnormal ejaculation.

Very rare: priapism.

**Respiratory, thoracic and mediastinal disorders**

Uncommon: rhinitis.
Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, urticaria.

Rare: angioedema.

Vascular disorders

Uncommon: postural hypotension.

During cataract surgery, a variant of small pupil syndrome known as Intra-operative Floppy Iris Syndrome (IFIS) has been reported during post-marketing surveillance in association with α1-adrenoceptor antagonist therapy (See PRECAUTIONS).

Post-marketing adverse events

The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency.

Vision disorders: blurred vision, vision impairment.

Skins and subcutaneous tissue disorders: skin desquamation, dermatitis exfoliative, erythema multiforme.

Respiratory, thoracic and mediastinal disorders: epistaxis.

Interactions

Medicines known to interact with tamsulosin

Concomitant cimetidine leads to a rise in plasma levels of tamsulosin, while furosemide leads to a fall (about 12% following a single 20 mg intravenous dose). However, as levels remain within the normal range, dosage need not be adjusted.

Concurrent administration of TAMSULOSIN HYDROCHLORIDE capsules with other α1-adrenoceptor antagonists is contraindicated because of the potential for hypotensive effects - see "CONTRAINDICATIONS".

Medicines which may interact with tamsulosin

Tamsulosin binds extensively to plasma proteins and may displace other protein-bound medicines. Clinical trial data are not available.

No interactions at the level of hepatic metabolism have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked metabolising enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

Medicines which do not interact significantly with tamsulosin

TAMSULOSIN HYDROCHLORIDE did not affect the pharmacokinetics of a single intravenous dose of digoxin 0.5 mg.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline.
**General**

Tamsulosin is metabolised in the liver, and may be expected to interact with other hepatically-metabolised drugs. Pharmacokinetic studies in healthy volunteers revealed that concomitant administration with strong inhibitors of CYP3A4 or CYP2D6 may lead to increased exposure to tamsulosin. Concomitant administration with ketoconazole (a known CYP3A4 inhibitor) resulted in an increased $C_{\text{max}}$ and AUC of tamsulosin. Tamsulosin should not be used in combination with strong inhibitors of CYP3A4 in patients known to be CYP2D6 poor metabolisers. Concomitant administration with paroxetine (a known CYP2D6 inhibitor) resulted in an increased $C_{\text{max}}$ and AUC of tamsulosin. Tamsulosin should therefore be used with caution in patients who are taking other drugs, particularly those which undergo hepatic metabolism.

**Other in vitro findings**

In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide and chlormadinone.

An in vitro study using human liver microsomal fractions showed no effect of amitriptyline, salbutamol, glibenclamide and finasteride on the rate of disappearance of tamsulosin. The clinical relevance of these findings is uncertain.

**Overdosage**

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.

If acute hypotension occurs after overdosage, cardiovascular support should be given and maintained. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this is insufficient then volume expanders and, when necessary, vasopressors could be administered. 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 to impede absorption, such as emesis, can be taken. When large quantities of tamsulosin are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

TAMSULOSIN HYDROCHLORIDE capsules are a modified release formulation. The signs and symptoms of overdose may be delayed or prolonged from the time of ingestion.

**Pharmaceutical Precautions**

None.

**Incompatibilities**

None known.

**Special Precautions For Storage**

Store below 25°C.
Shelf-Life

TAMSULOSIN HYDROCHLORIDE 0.4 mg modified release capsules can be used up to two years after manufacture. The expiry date is printed on the package.

Medicine Classification

Prescription Medicine.

Package Quantities

Cartons containing 30 and 90 capsules

Further Information

List of excipients

TAMSULOSIN HYDROCHLORIDE 0.4 mg modified release capsules contain the following excipients:

- Microcrystalline Cellulose
- Methacrylic-acid - ethyl acrylate copolymer
- Polysorbate 80
- Sodium lauril sulfate
- Triacetin
- Calcium Stearate
- Talc
- Hard gelatin
- Indigotine E132
- Titanium dioxide E171
- Yellow iron oxide E172
- Red iron oxide E172

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Date of Preparation

05 August 2014

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