

Harnal OCAS[®] 0.4 mg tablets

1. Name of the medicinal product

Harnal OCAS[®] 0.4 mg tablets

2. Qualitative and quantitative composition

Each prolonged release film-coated tablet contains 0.4 mg tamsulosin hydrochloride.

For excipients, see section 6.1.

3. Pharmaceutical form

Film-coated, prolonged release tablets.
(Oral Controlled Absorption System, OCAS).

Approximately 9 mm in diameter, round, bi-convex, yellow, film-coated and debossed with the code '04'.

4. Clinical particulars

4.1 Therapeutic indications

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Oral use.

One tablet daily.

Harnal OCAS[®] 0.4 mg tablets can be taken independently of food.

The tablet must be swallowed whole and not be crunched or chewed as this interferes with the prolonged release of the active substance.

No dose adjustment is warranted in renal impairment.

No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency.

There is no relevant indication for use of Harnal OCAS[®] 0.4 mg tablets in children.

4.3 Contra-indications

- Hypersensitivity to tamsulosin hydrochloride, including drug-induced angioedema or to any of the excipients.
- A history of orthostatic hypotension.
- Severe hepatic insufficiency.

4.4 Special warnings and special precaution for use

As with other α_1 -adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS[®] 0.4 mg tablets, 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.

Before therapy with Harnal OCAS[®] 0.4 mg tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

The treatment of patients with severe renal impairment (creatinine clearance of <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 and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery.

The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (see section 4.5).

Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administering tamsulosin hydrochloride.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, while furosemide a fall, but as levels remain within the normal range posology need not to be adjusted.

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. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin hydrochloride. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and C_{max} of tamsulosin hydrochloride by a factor of 2.8 and 2.2, respectively. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.

Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a C_{max} and AUC of tamsulosin that had increased by a factor of 1.3 and 1.6, respectively, but these increases are not considered clinically relevant.

Concurrent administration of other α_1 -adrenoceptor antagonists could lead to hypotensive effects.

4.6 Pregnancy and lactation

Not applicable, as Harnal OCAS[®] 0.4 mg tablets is intended for male patients only.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be aware of the fact that dizziness can occur.

4.8 Undesirable effects

MedDRA system organ class	Common (>1%, <10%)	Uncommon (>0.1%, <1%)	Rare (>0.01%, <0.1%)	Very rare (<0.01%)
Cardiac disorders		Palpitations		
Gastro-intestinal disorders		Constipation, Diarrhoea, Nausea, Vomiting		
General disorders and administration site conditions		Asthenia		
Nervous system disorders	Dizziness (1.3%)	Headache	Syncope	
Reproductive system and breast disorders	Ejaculation disorders			Priapism
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Skin and		Rash, Pruritus,	Angioedema	Steven-

subcutaneous tissue disorders		Urticaria		Johnson syndrome
Vascular disorders		Orthostatic hypotension		

Post-marketing experience

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.

During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported during post-marketing surveillance (see also section 4.4).

Skin and subcutaneous tissue disorders: dermatitis exfoliative, erythema multiforme, photosensitivity reaction.

Respiratory, thoracic and mediastinal disorders: epistaxis.

General disorders: chest discomfort that could be caused or associated with other medical conditions such as respiratory conditions or cardiac disease.

In addition to the adverse events listed above, atrial fibrillation, arrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use. However, the role of tamsulosin in their causation cannot be reliably determined.

4.9 Overdose

Symptoms

Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

Treatment

In case of acute hypotension occurring after overdosage, cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help, then volume expanders and, when necessary, vasopressors could be employed. 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, 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

α_1 -adrenoceptor antagonists.

ATC code: G04CA02. Preparations for the exclusive treatment of prostatic disease.

Mechanism of action

Tamsulosin binds selectively and competitively to the postsynaptic α_1 -adrenoceptors, in particular to subtypes α_{1A} and α_{1D} . It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects

Harnal OCAS[®] 0.4 mg tablets increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra thereby improving voiding symptoms.

It also improves the storage 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 surgery or catheterisation is significantly delayed.

α_1 -adrenoceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Harnal OCAS[®] 0.4 mg tablets.

5.2 Pharmacokinetic properties

Absorption

Harnal OCAS[®] 0.4 mg tablets is a prolonged release tablet of the non-ionic gel matrix type. The OCAS formulation provides consistent slow release of tamsulosin, resulting in an adequate exposure, with little fluctuation, over 24 hours.

Tamsulosin administered as Harnal OCAS[®] 0.4 mg tablets is absorbed from the intestine. Under fasting conditions, approximately 57% of the administered dose is estimated to be absorbed.

The rate and extent of absorption of tamsulosin administered as Harnal OCAS[®] 0.4 mg tablets are not affected by a low-fat meal. The extent of absorption is increased by 64% and 149% (AUC and C_{max} , respectively) by a high-fat meal compared to fasted.

Tamsulosin shows linear pharmacokinetics.

After a single dose of Harnal OCAS[®] 0.4 mg tablets in the fasted state, plasma concentrations of tamsulosin peak at a median time of 6 hours. In steady state, which is reached by day 4 of multiple dosing, plasma concentrations of tamsulosin peak at 4 to 6 hours, in the fasted and fed state. Peak plasma concentrations increase from approximately 6 ng/ml after the first dose to 11 ng/ml in steady state.

As a result of the prolonged release characteristics of Harnal OCAS[®] 0.4 mg tablets the trough concentration of tamsulosin in plasma amounts to 40% of the peak plasma concentration under fasted and fed conditions.

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

Distribution

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

Metabolism

Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged active substance. It is metabolised in the liver.

In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.

In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin hydrochloride metabolism by other CYP isozymes. Inhibition of CYP3A4 and CYP2D6 drug metabolising enzymes may lead to increased exposure to tamsulosin hydrochloride (see sections 4.4 and 4.5).

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

Excretion

Tamsulosin and its metabolites are mainly excreted in the urine. The amount excreted as unchanged active substance is estimated to be about 4-6% of the dose, administered as Harnal OCAS[®] 0.4 mg tablets.

After a single dose of Harnal OCAS[®] 0.4 mg tablets and in steady state, elimination half-lives of about 19 and 15 hours, respectively, have been measured.

5.3 Preclinical safety data

Single and repeat dose toxicity studies were performed in mice, rats and dogs. In addition, reproduction toxicity in rats, carcinogenicity in mice and rats and *in vivo* and *in vitro* genotoxicity were examined.

The general toxicity profile, as seen with high doses of tamsulosin, is consistent with the known pharmacological actions of the α_1 -adrenoceptor antagonists.

At very high dose levels, the ECG was altered in dogs. This response is considered to be not clinically relevant. Tamsulosin showed no relevant genotoxic properties.

Increased incidences of proliferative changes of mammary glands of female rats and mice have been reported. These findings, which are probably mediated by hyperprolactinemia and only occurred at high dose levels, are regarded as irrelevant.

6. Pharmaceutical particulars

6.1 List of excipients

Macrogol 7.000.000.

Macrogol 8.000.

Magnesium stearate (E470b).

Butylhydroxytoluene (E321).

Colloidal silica anhydrous (E551).

Hypromellose (E464).

Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Aluminium/aluminium foil blister packs containing 30 tablets.

6.6 Instructions for use and handling

No special requirements.

Manufactured by:

Delpharm Meppel B.V.
Meppel, The Netherlands

Imported by:

Astellas Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

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