

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1244/002/001

Case No: 2053052

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Astellas Pharma Europe BV

Elisabethhof 19, 2353 EW LEIDERDORP, Netherlands

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Hystream 400 micrograms modified release capsules, hard

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **04/11/2008**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hystream 400 micrograms modified release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains as active ingredient tamsulosin hydrochloride 0.4 mg.

Excipient(s):

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release capsule, hard

Orange/olive-green coded 0.4 and 701

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

The capsule must be swallowed whole and must not be crunched or chewed, as this interferes with the modified release of the active ingredient.

No dose adjustment is warranted in renal impairment. No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see also section 4.3, Contraindications).

There is no relevant indication for use of Hystream 400 micrograms in children.

4.3 Contraindications

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 precautions for use

As with other α_1 -adrenoceptors antagonists, a reduction in blood pressure can occur in individual cases during treatment with Hystream 400 micrograms, 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 Hystream 400 micrograms 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 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 in patients for whom cataract surgery is scheduled is not recommended.

Discontinuing tamsulosin 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.

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 in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

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

In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinon, 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 chlormadinon.

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 drug metabolizing enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

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

4.6 Pregnancy and lactation

Not applicable as Hystream 400 micrograms 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

System Organ Class	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10,000,<1/1000	Very rare <1/10,000
Nervous system disorders	dizziness (1.3%)	headache	syncope	
Cardiac disorders		palpitations		
Vascular disorders		postural hypotension		
Respiratory, thoracic and mediastinal disorders		rhinitis		
Gastrointestinal disorders		constipation, diarrhoea, nausea, vomiting		
Skin and subcutaneous tissue disorders		rash, pruritus, urticaria	angioedema	
Reproductive system and breast disorders		abnormal ejaculation		priapism
General disorders and administration site conditions		asthenia		

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 (see also section 4.4, special warnings and precautions for use).

4.9 Overdose

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.

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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: α_1 -adrenoceptor antagonist, ATC code: GO4C AO2. 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:

Hystream 400 micrograms 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 catheterization is significantly delayed.

α 1-adrenoceptors antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Hystream 400 micrograms.

5.2 Pharmacokinetic properties*Absorption:*

Tamsulosin is absorbed from the intestine and is almost completely bioavailable. Absorption of tamsulosin is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking Hystream 400 micrograms after the same meal. Tamsulosin shows linear kinetics.

After a single dose of Hystream 400 micrograms 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, C_{max} 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 man, tamsulosin is about 99% bound to plasma proteins. The volume of distribution is small (about 0.2 l/kg).

Biotransformation:

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

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

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

Elimination:

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

After a single dose of Hystream 400 micrograms in the fed state and in the steady state in patients, elimination half-lives of about 10 and 13 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 -adrenoceptors 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

Capsule content

Microcrystalline Cellulose E460
Methacrylic acid - ethyl acrylate copolymer (1:1)
Polysorbate 80 E433
Sodium laurilsulfate
Triacetin E1518
Calcium Stearate E470a
Talc E553b

Capsule shell

Hard gelatin
Indigotine E132
Titanium dioxide E171
Yellow iron oxide E172
Red iron oxide E172

Printing ink

Shellac E904
Black iron oxide (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Polypropylene-aluminium blister packs containing 10 capsules per strip; cardboard boxes containing 10, 20, 30, 50, 60, 90, 100 and 200 capsules.

PVC/PVDC-aluminium blister packs containing 5 capsules per strip; cardboard boxes containing 50 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe BV
Elisabethhof 19
2353 EW Leiderdorp
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1244/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 2005

Date of last renewal: 12 July 2006

10 DATE OF REVISION OF THE TEXT

November 2008