IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1304/001/001
Case No: 2045363

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

Biokanol Pharma GmbH

Kehler Strasse 7, **76437 Rastatt**, **Germany**

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

Tamsulas 400 micrograms Prolonged 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 **13/05/2008** until **12/05/2013**.

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

Tamsulas 400 micrograms prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 micrograms of tamsulosin hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Orange no 2 gelatin capsule which contains white or yellowish granules.

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

One capsule daily, to be taken after breakfast or after the first meal of the day.
The capsule should be swallowed whole with a glass of water in sitting or standing position (not in lying position). The capsule should not be broken or chewed as this will interfere with the modified release of the active ingredient. In cases when patients have difficulty swallowing (e.g. dysphagia), the capsule may be opened and the contents swallowed without chewing.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

A reduction in blood pressure can occur in individual cases during treatment with tamsulosin 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 tamsulosin is initiated the patients 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 severely renally impaired patients (creatine clearance of less than 10 ml/min) should be approached with caution as these patients have not been studied.

Angio-oedema has been rarely reported after the use of tamsulosin. Treatment should be discontinued immediately, patient should be monitored until disappearance of the oedema, and tamsulosin should not be re-administered.

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. Isolated reports have also been received with other aplpha- 1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during cataract surgery operation currently or past use of alpha -1 blockers should be made known to opthalmic surgeon in advance of surgery.

The benefit of stopping tamsulosin therapy prior to cataract surgery has not yet been established,

The initiation of tamsulosin therapy in patients awaiting cataract surgery is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been observed when tamsulosin was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant cimetidine raises, and concomitant furosemide lowers plasma concentrations of tamsulosin but, as the concentration of tamsulosin remains within the normal range, posology needs to be altered. 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 have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked metabolizing enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin may increase the elimination rate of tamsulosin.
Concurrent administration of other a1-adrenoceptor antagonists may lead to hypotensive effects.

4.6 Pregnancy and lactation

Tamsulosin is intended for males 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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders:
Common (>1/100, <1/10): Dizziness
Uncommon (>1/1,000, <1/100): Headache
Rare (>1/10,000, <1/1,000): Syncope

Eye disorders
Common (>1/100, <1/10): Floppy Iris Syndrome (IFIS, variant of small pupil syndromes during cataract surgery)

Cardiac disorders:
Uncommon (>1/1,000, <1/100): Tachycardia

Vascular disorders:
Uncommon (>1/1,000, <1/100): Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon (>1/1,000, <1/100): Rhinitis

Gastrointestinal disorders:
Uncommon (>1/1,000, <1/100): Constipation, diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders:
Uncommon (>1/1,000, <1/100): rash, itching, urticaria
Rare (>1/10,000, <1/1,000): Angiooedema

Reproductive system and breast disorders:
Uncommon (>1/1,000, <1/100): Abnormal ejaculation
Very rare (<1/10,000): Priapism

General disorders and administration site conditions:
Uncommon (>1/1,000, <1/100): Asthenia

4.9 Overdose

No cases of acute overdosage have been reported. However, acute hypotension could theoretically occur after overdosage in which case 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 measure applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

If large quantities of the medicinal product are involved, gastric lavage may be performed and activated charcoal and an osmotic laxative, such as sodium sulphate, may be give.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha-adrenoreceptor antagonists, ATC code: G04CA02

Mechanism of action

Tamsulosin binds selectively and competitively to postsynaptic α_{1A} adrenoreceptors, which convey smooth muscle contraction, thereby relaxing prostatic and urethral smooth muscle.

Pharmacodynamic effects

Tamsulosin increase the maximum urinary flow rate by relaxing prostatic and urethral smooth muscle, thus relieving obstruction.

The medicinal product also improves the irritative and obstructive symptoms in which the contraction of smooth muscle in the lower urinary tract plays an important role.

Alpha-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin in normotensive patients.

The medicinal product’s effect on storage and voiding symptoms are also maintained during long-term therapy, as a result of which the need for surgical treatment is significantly postponed.

5.2 Pharmacokinetic properties

Absorption

Tamsulosin is rapidly absorbed from the intestine and its bioavailability is almost complete. Absorption is slowed down if a meal has been eaten before taking the medicinal product. Uniformity of absorption can be assured by always taking tamsulosin after breakfast.
Tamsulosin shows linear kinetics.

Peak plasma levels are achieved at approximately six hours after a single dose of tamsulosin taken after a full meal. The steady state is reached by day five of multiple dosing, when Cmax in patients is about two-thirds higher than that reached after a single dose. Although this has been demonstrated only in the elderly, the same result would also be expected in younger patients.
There are huge inter-patient variations in plasma levels of tamsulosin, both after single as well as multiple dosing.

Distribution

In humans, tamsulosin is more than 99% bound to plasma proteins and the volume of distribution is small (about 0.21/kg).

Biotransformation

Tamsulosin has a low first pass metabolic effect. Most tamsulosin is found unaltered in plasma. The substance is metabolised in the liver.

In studies on rats, tamsulosin was found to cause only a slight induction of microsomal liver enzymes.

The metabolites are not as effective and toxic as the active medicinal product itself.

Excretion

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

The elimination half-life of tamsulosin in patients is approximately 10 hours (when taken after a meal) and 13 hours in a steady state.

5.3 Preclinical safety data

Toxicity after a single dose and multiple dosing has been investigated in mice, rats and dogs. Reproductive toxicity has also bee investigated in rats, carcinogenicity in mice and rats, and genotoxicity *in vivo* and *in vitro*.

The common toxicity profile found with large doses of tamsulosin is equivalent to the pharmacological effect associated with alspha adrenergic antagonists.
Changes in ECG readings were found with very large doses in dogs. This is not, however, assumed to be of any clinical significance. Tamsulosin has not been found to have any significant genotoxic properties.

Greater proliferative changes in the mammary glands of female rats and mice have been discovered on exposure to tamsulosin. These findings, which are probably indirectly linked to hyperprolactinaemia and only occur as a result of large doses having been taken, are considered clinically insignificant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

capsule contents:

sodium alginate
methacrylic acid-ethyl acrylate copolymer 1:1
glycerol dibehenate
maltodextrin
sodium laurilsulphate
macrogol 6000
polysorbate 80
sodium hydroxide
simeticone emulsion (*simeticone, methylcellulose, sorbic acid*)
silica, colloidal anhydrous

capsule shell:

gelatin
red iron oxide (E172)
titanium dioxide (E171)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store in the original container.
Do not store above 30°C.

6.5 Nature and contents of container

Blister: PVC/PVDC/Al-blister

Blisters are packed in cardboard cartons.

Capsule container: HDPE-container with PP-cap

Pack sizes: 20,50, 100 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

Biokanol Pharma GmbH
Kehler Strasse 7
76437 Rastatt
Germany
Tel: +49 7222786794
Fax: +49 7222786799
e-mail: swh@biokanol.de

8 MARKETING AUTHORISATION NUMBER

PA 1304/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th April 2007

10 DATE OF REVISION OF THE TEXT

September 2007