IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0711/087/001
Case No: 2016164

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

Rowex Ltd

Bantry, **Co Cork**, , **Ireland**

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

Tamsulosin 400 microgram modified release capsule

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 **16/03/2006** until **15/03/2011** .

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tamsulosin 400microgram modified release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release capsule contains 400microgram tamsulosin hydrochloride
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule-hard, filled with gastro resistant prolonged release granules.

A size 2 capsule with orange body and olive green cap, coded 0.4 in black

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of adminstration

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 crunched or chewed as this will interfere with the modified release of the active ingredient.

4.3 Contraindications

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

A history of orthostatic hypotension.

Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other alpha$_{1}$- blockers, a reduction in blood pressure can occur in individual cases during treatment with Tamsulosin 0.4, 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 0.4 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 severely renally impaired patients (creatinine clearance of less than 10ml/min) should be approached with caution as these patients have not been studied.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been seen when Tamsulosin 0.4 was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, and furosemide a fall, but as levels remain within the normal range posology need not be changed.

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 P_{450}-linked drug metabolising 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 Tamsulosin 0.4 is intended for male patients only.

4.7 Effects on ability to drive and use machines

No data is available on whether Tamsulosin 0.4 adversely affects the ability to drive or operate machines. However, in this respect patients should be aware of the fact that dizziness can occur.

4.8 Undesirable effects

Common (>1%, <10%)
Nervous system disorders: dizziness (1.3%)
Uncommon (>0.1%, <1%)
Nervous system disorders: headache
Cardiac disorders: palpitations
Vascular disorders: postural hypotension
Respiratory, thoracic and mediastinal disorders: rhinitis
Gastrointestinal disorders: constipation, diarrhoea, nausea, vomiting
Skin and subcutaneous disorders: rash, pruritus, uticaria
Reproductive system and breast disorders: abnormal ejaculation
General disorders and administration site conditions: asthenia
Rare (>0.01%, <0.1%)
Nervous system disorders: syncope
Skin and subcutaneous disorders: angioedema
Very rare (<0.01%)
Reproductive system and breast disorders: priapism

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 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:

Alpha$_1$-adrenoceptor antagonist.
ATC code: G04C A02.Preparations for the exclusive treatment of prostatic disease.

Mechanism of action:

Tamsulosin binds selectively and competitively to the postsynaptic alpha$_1$-receptors, in particular to the subtypes alpha$_{1A}$ and alpha $_{1D}$. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects:

Tamsulosin 0.4 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.
Alpha$_1$-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Tamsulosin 0.4.

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 Tamsulosin 0.4 after the same meal.

Tamsulosin shows linear kinetics.

After a single dose of Tamsulosin 0.4 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 and volume of distribution is small (about 0.2 l/kg).

Biotransformation:

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

In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin. No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see also section 4.3).
None of the metabolites are more active than the original 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 drug.

After a single dose of Tamsulosin 0.4 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 studies 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 alpha-adrenergic blocking agents.

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 hyperprolactinaemia and only occurred at high dose levels are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Calcium hydrogen phosphate anhydrous
Methacrylic acid-ethyl acrylate copolymer (1:1)
Polysorbate 80
Sodium lauril sulfate
Methacrylic acid copolymer, type C
Triethyl citrate
Colloidal anhydrous silica
Sodium hydrogen carbonate
Talc
Titanium dioxide (E171)
Simethicone

Capsule shell

Gelatin
Indigo carmine FD&C blue 2 (E132)
Ferric oxide, black (E172)
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
Purifed water

Capsule body

Gelatin
Ferric oxide, red (E172)
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
Purified water

Printing ink

Shellac
Propylene glycol
Potassium hydroxide
Ferric oxide, black (E172)

6.2 Incompatibilities

None known.

6.3 Shelf Life

Blister AL/PVC: 18months
Blister Al/Al: 2years

6.4 Special precautions for storage

Do not store above 30^{o}C

6.5 Nature and contents of container

The capsules are available in Al/PVC or Al/Al blister packs in sizes of 10 or 30 capsules. Medical samples of 10 capsules are also available.
Not all pack size 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

Rowex Ltd
Bantry
County Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/87/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 16th March 2006.

10 DATE OF REVISION OF THE TEXT