SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BENIPROSIN SR (Capsule 0,4 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BENIPROSIN SR

Each capsule contains tamsulosin hydrochloride 0,4 mg

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule

Brown, opaque cap/ orange opaque body, of size '2' imprinted with 'R' on cap and 'TSN400' on body in black edible ink, containing white to off-white granular beads.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

BENIPROSIN SR capsules are indicated for the treatment of functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and Method of Administration

Method of administration

One 0,4 mg of BENIPROSIN SR capsule to be taken daily after breakfast or after first daily meal

BENIPROSIN SR capsules should be swallowed whole with water (about 150 ml) in the standing or sitting position.

BENIPROSIN SR capsules should not be crushed or chewed, as this will interfere with the sustained release property of this active ingredient.

4.3 Contraindications:

BENIPROSIN SR capsules are contra-indicated in the following conditions:

- In patients hypersensitive to tamsulosin hydrochioride or any other components of the product.
- A history of orthostatic hypotension.
- Hepatic insufficiency.
- Micturition syncope history
- Should not be used in combinations with strong inhibitors of CYP3A4 eg ketoconazole (See section 4.5)

4.4 Special warnings and precautions for use

A decrease in blood pressure with orthostatic hypotension and syncope may occur during treatment with **BENIPROSIN SR.** At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared.

Before therapy with **BENIPROSIN SR** 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.

Angioedema has been rarely reported after the use of tamsulosin. In case of angioedema, .treatment should be discontinued immediately, the patient should be monitored until disappearance of the oedema, and tamsulosin should not be re-administered

The “Intraoperative Floppy Iris Syndrome” (IFIS) is a variant of small pupil syndrome and is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive inoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions

The “Intraoperative Floppy Iris Syndrome” (IFIS) has been observed during cataract and glaucoma surgery in some patients treated with alpha-1 blockers, including **BENIPROSIN SR**.). Most reports were in patients taking the alpha-1 blocker when IFIS occurred, but in some cases, the alpha-1 blocker had been stopped prior to surgery. In most of these cases, the alpha-1-blocker had been stopped recently prior to surgery (2 to 14 days), but in a few cases, IFIS was reported after the patient had been off the alpha-1 blocker for a longer period (5 weeks to 9 months

The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances.

The initiation of therapy with BENIPROSIN SR 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 BENIPROSIN SR in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

BENIPROSIN SR should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

BENIPROSIN SR should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (see section 4.5).

BENIPROSIN SR is intended for adult male patients only.

4.5 Interaction with other medicines and other forms of Interaction

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

Concomitant administration with cimetidine increases plasma levels of tamsulosin and concomitant administration with furosemide decreases the plasma levels of tamsulosin, but as levels remain within the normal range, dosage need not be changed.

In vitro neither diazepam, propanolol, amitriptyline, diclofenac, giibenclamide, simvastatin and warfarin

change the free fraction of tamsulosin in human plasma.

Neither does tamsulosin change the free fractions of diazepam, propranolol, thrichlormethazide and chlormadinon

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 Cmax 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 given 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 Cmax 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 alpha$_1$-adrenoceptor antagonists could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

BENIPROSIN SR capsules should not be used in females.

Ejaculation disorders have been observed in short and long term clinical studies with tamsulosin. Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported in the post authorization phase.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness which may affect the ability to drive or operate machinery may occur.

4.8 Undesirable effects

MedDRA	Frequent	Less Frequent	Frequency

System Organ Class			**Unknown**
Nervous system disorders	- Dizziness	- Headaches - -Syncope	
Eye disorders			-Blurred Vision -Visual impairment
Cardiac Disorders		- Palpitations	-Atrial Fibrillation -Arrhythmia -Tachycardia -Dyspnoea
Vascular Disorders		- Orthostatic hypotenson	
Respiratory, thoracic and mediastinal disorders		- Rhinitis	-Epitaxis
Gastrointestinal disorders		- Vommiting - Constipation - Nause - Diarrhoea	-Dry mouth

***Skin and subcutaneous tissue* disorders**		- Rash - Pruritus - Urticaria - Angioedema - Steven Johnson syndrome	-Erythema multiforme -Exfoliative dermatitis
Reproductive system and breast disorders	-Ejaculation Disorders -Retrograde ejaculation -Ejaculation failure	-Priapism	
General disorders and administration site conditions:		-Aesthenia	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/

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 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:

A 34 Other

Pharmacotherapeutic category: Adrenergic α1-receptors antagonist.

ATC: G04CA02.

The product is designed exclusively for the treatment of diseases of the prostate.

Mechanism of action

Tamsulosin binds selectively and competitively to post-synaptic α1-adrenoreceptors, in particularly to the subtype alpha$_{1A}$ and alpha$_{1D}$ with relaxation of smooth muscle in the bladder neck and prostate, resulting in an improvement in urine flow rate. Alpha1-blockers reduce blood pressure by lowering peripheral resistance.

Pharmacodynamic properties

Tamsulosin increases the maximum urine flow rate. It relieves obstruction by relaxing the smooth muscle in the prostate and urethra.

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.

Alpha1- blockers can reduce blood pressure by lowering peripheral resistance. Tamsulosin is not

intended for use as an antihypertensive medicine.

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 improved by the patient always taking tamsulosin after the same meal.

After a single dose of tamsulosin taken after a meal, plasma levels of tamsulosin peaked at approximately 6 hours.

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 younger patients.

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, 21 L/kg).

Biotransformation

Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged medicine. 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 medicine metabolising enzymes may lead to increased exposure to tamsulosin hydrochloride (see section 4.4).

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

Excretion

Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of a dose being present as an unchanged drug. The elimination half-life after a single dose is about 10 hours. The elimination half-life in steady state is about 13 hours. The lowering of the dose in renal impairment is not warranted.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tamsulosin hydrochloride beads

Magnesium stearate, methycrylic acid-ethyl acrylate copolymer (1:1) dispersion, microcrystalline cellulose (PH101)

Enteric coating

Methycrylic acid-ethyl acrylate copolymer (1:1), sodium hydroxide, triacetin, talc,

Extra granular

Talc

Capsule Shell

Brown cap/Orange body size 2

Body composition

Brilliant blue (Cl No 42090), gelatin; poncrea 4R (Cl No 16255), quinolone yellow (Cl No 470005), sunset yellow (Cl No 15985), titanium dioxide (Cl No 77891**)**

Cap Composition

Brilliant blue (Cl No 42090), carmosine (Cl No14720), gelatin, titanium dioxide (Cl 77891); yellow iron oxide (Cl No 77891)

Printing Ink-1

Activated charcoal, alcohol (ethanol)[#], isopropyl alcohol[#], shellac

Printing Ink-2 & 3

Tekprint SW-9007 or Tekprint SW-9008

Black iron oxide (E172), butyl alcohol, dehydrated alcohol, isopropyl alcohol,

potassium hydroxide, propylene glycol, shellac, strong ammonia solution

[#] Used as solvent an lost during processing

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C in the original package,

protected from moisture.

6.5 Nature and contents of container

Cartons containing 10, 30 or 60 capsules packed in blister strips. The blister strip consists of clear, transparent film of PVC coated with PVdC with a backing of aluminium foil.

6.6 Special precautions for disposal

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals {Pty) Ltd

14 Lautre Road,

Stormill Ext 1

Roodepoort,

1724

South Africa

8.REGISTRATION NUMBER(S)

9.DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 December 2008

10.DATE OF REVISON OF THE TEXT

20th October 2021