TAMSULOSIN 0,4 BIOTECH
(Each capsule contains 0,4 mg tamsulosin hydrochloride
42/18.10/0478-– registered)

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TAMSULOSIN 0,4 BIOTECH, sustained release, capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TAMSULOSIN 0,4 BIOTECH capsule contains: 0,4 mg tamsulosin hydrochloride.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sustained release capsules

TAMSULOSIN 0,4 BIOTECH capsules are yellow (body) and light-green (cap) in colour. The mark 'TML 0,4' is printed on the capsule in black. The capsules contain white to slightly yellowish pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TAMSULOSIN 0,4 BIOTECH is indicated for the treatment of functional symptoms of benign prostatic hyperplasia (BPH) in adult males.

Efficacy in children with neurogenic bladder has not been demonstrated.

4.2 Posology and method of administration

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Posology

One TAMSULOSIN 0,4 BIOTECH sustained release capsule to be taken daily after breakfast.

Method of administration

Oral administration

TAMSULOSIN 0,4 BIOTECH should be swallowed whole with water (about 150 ml) in the standing or sitting position.

TAMSULOSIN 0,4 BIOTECH should not be crunched or chewed, as this will interfere with the sustained release property of the active ingredient.

4.3 Contraindications

TAMSULOSIN 0,4 BIOTECH is contra-indicated in the following conditions:

- In patients hypersensitive to tamsulosin hydrochloride or to any of the excipients of TAMSULOSIN 0,4 BIOTECH, listed in section 6.1.
- A history of orthostatic hypotension.
- Hepatic insufficiency.
- TAMSULOSIN 0,4 BIOTECH should not be used in combination with strong inhibitors of CYP3A4, e.g., 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 TAMSULOSIN 0,4 BIOTECH. 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 BIOTECH 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.

Rarely (probably less than one in fifty thousand patients), TAMSULOSIN 0,4 BIOTECH, like other $alpha_1$ antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition.

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 0,4 BIOTECH. IFIS may lead to increased procedural complications during the operation. The initiation of therapy with TAMSULOSIN 0,4 BIOTECH in patients for whom cataract surgery is scheduled is not recommended.

Discontinuing TAMSULOSIN 0,4 BIOTECH, 1 to 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of requirement of stopping the 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 0,4 BIOTECH in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

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***Special precautions*:**

TAMSULOSIN 0,4 BIOTECH should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

TAMSULOSIN 0,4 BIOTECH should be used with caution in combination with strong and moderate (e.g., erythromycin) inhibitors of CYP3A4 (see section 4.5).

TAMSULOSIN 0,4 BIOTECH 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 0,4 BIOTECH was given concomitantly with atenolol, enalapril, nifedipine or theophylline.

Concomitant administration with cimetidine increases plasma levels of TAMSULOSIN 0,4 BIOTECH and concomitant administration with furosemide decreases the plasma levels of TAMSULOSIN 0,4 BIOTECH, but as levels remain within the normal range, dosage need not be changed.

Diazepam, propranolol, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin do not change the free fraction of tamsulosin in human plasma, *in vitro.* Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide and chlormadinone.

No interactions at the level of hepatic metabolism have been observed during *in vitro* studies with liver microsomal fractions (representative of the cytochrome P450- linked drug metabolising enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride.

Diclofenac and warfarin, however, may increase the elimination rate of TAMSULOSIN 0,4 BIOTECH.

Concomitant administration of TAMSULOSIN 0,4 BIOTECH with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin. 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 0,4 BIOTECH should not be given in combination with strong inhibitors of CYP3A4 (see section 4.3) in patients with poor metaboliser CYP2S6 phenotype.

TAMSULOSIN 0,4 BIOTECH should be used with caution in combination with moderate (e.g., erythromycin) inhibitors of CYP3A4.

Concomitant administration of TAMSULOSIN 0,4 BIOTECH 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 alpha$_1$-adrenoceptor antagonists and anaesthetic medicines could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

TAMSULOSIN 0,4 BIOTECH should not be used in females.

Fertility

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 authorisation phase.

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4.7 Effects on ability to drive and use machines

No data is available on whether TAMSULOSIN 0,4 BIOTECH adversely affects the ability to drive or operate machines.

Patients should be aware of the fact that drowsiness, blurred vision, dizziness and syncope can occur.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA System Organ Class

Nervous system disorders	
Frequent:	Dizziness
Less frequent:	Headache, syncope
Eye disorders	
Frequency unknown:	Vision blurred*, visual impairment*
Cardiac disorders	
Less frequent:	Palpitations
Vascular disorders	
Less frequent:	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorder	
Less frequent:	Rhinitis
Frequency unknown:	Epistaxis*
Gastrointestinal disorders	
Less frequent:	Constipation, diarrhoea, nausea, vomiting
Frequency unknown:	Dry mouth*
Skin and subcutaneous tissue disorders	

Less frequent:	Rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome
Frequency unknown:	Erythema multiforme *, dermatitis exfoliative*
Reproductive systems and breast disorders	
Frequent:	Ejaculation disorders, including retrograde ejaculation and ejaculation failure
Less frequent:	Priapism
General disorders and administration site disorders	
Less frequent:	Asthenia

*Observed post-marketing

Drowsiness, blurred vision or oedema can occur.

During cataract surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of TAMSULOSIN 0,4 BIOTECH during post-marketing surveillance (see section 4.4).

In addition to the adverse events listed above, atrial fibrillation, dysrhythmia, tachycardia and dyspnoea have been reported in association with TAMSULOSIN 0,4 BIOTECH use.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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Symptoms

No cases of acute overdosage have been reported. However, acute hypotension could theoretically occur after overdosage in which case cardiovascular support should be given.

Severe hypotensive effects have been observed at different levels of overdosing.

Treatment

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 0,4 BIOTECH is very highly bound to proteins. Measures such as emesis, can be taken to impede absorption.

When large quantities are involved, activated charcoal and an osmotic laxative, such as sodium sulphate can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A18.10 Other.

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52.

Tamsulosin, a benzenesulfonamide, is an alpha$_1$-adrenergic blocking agent which binds selectively and competitively to the postsynaptic alpha$_1$ adrenoceptors in particular to the subtype alpha$_{1A}$, and alpha$_{10}$ with relaxation of smooth muscle in the bladder-neck and prostate, resulting in an improvement in urine flow rate. Alpha$_1$-blockers reduce blood pressure by lowering peripheral resistance.

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 play 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.

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 [breakfast] 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, 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 younger patients.

There is 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 the form of unchanged drug. It is metabolized 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 medicine metabolizing enzymes may lead to increased exposure to Tamsulosin hydrochloride (see sections 4.4 and 4.5).

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

Elimination:

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

Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30% (Eudragit L 30 D-55)

Microcrystalline cellulose

Polyacrylate dispersion 30% (Eudragit NE 30 D)

Polysorbate

Sodium lauryl sulphate

Talc

Capsule composition

Body:

Gelatin,

Red iron oxide (E172)

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Titanium dioxide (E171)

Yellow iron oxide (E172).

Cap:

Black iron oxide (E172)

Gelatin

Patent blue V (E131)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Black ink:

Black iron oxide (E172)

Butyl alcohol

Dehydrated alcohol

Isopropyl alcohol

Potassium hydroxide

Purified water

Shellac

Strong ammonia sol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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Store in the original packaging, at or below 25 °C. Protect from moisture.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

TAMSULOSIN 0,4 BIOTECH capsules are available in blister strips with a silver aluminium side and a clear PVDC/TE/PVC side. The blister strips are packed in cartons. The cartons contain 10, 30, 60 or 100 capsules. All sizes may not be marketed at one time.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Halfway house

Midrand

1685

8 REGISTRATION NUMBER

42/18.10/0478

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of Registration: 04 December 2009.

10 DATE OF REVISION OF THE TEXT

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