SCHEDULING STATUS
South Africa: S4
Namibia: NS2
Kenya: POM
Botswana: Schedule 2

PROPRIETARY NAME AND DOSAGE FORM
Flomax 0,4 SR Sustained Release Capsule

COMPOSITION
Active ingredient:
Each capsule contains 0,4 mg tamsulosin hydrochloride
Excipients:
Capsule content: microcrystalline cellulose, methacrylic acid – ethy acrylate copolymer, polysorbate 80, sodium laurylsulfate, triacetin, calcium stearate, talc
Capsule shell: hard gelatine, indigotine E132, titanium dioxide E171, yellow iron oxide E172, red iron oxide E172
Printing ink: shellac, propylene glycol, black iron oxide E172

PHARMACOLOGICAL CLASSIFICATION
A 34 Other

PHARMACOLOGICAL ACTION
Tamsulosin binds selectively and competitively to the postsynaptic $alpha_1$-adrenoceptors in particular to the subtype $alpha_{1A}$ and $alpha_{1D}$. It brings about relaxation of the prostatic and urethral smooth muscle.
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.
$Alpha_1$- blockers can reduce blood pressure by lowering peripheral resistance. Tamsulosin is not intended for use as an antihypertensive medicine.
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 0,4 mg capsule after the same meal. After a single dose of tamsulosin 0,4 mg capsule taken after a meal, plasma levels of tamsulosin peak at around 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 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 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 WARNINGS AND INTERACTIONS).
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 in the form of unchanged medicine. The elimination half-life after a single dose is about 10 hours. The

elimination half-life in the steady state is about 13 hours. The lowering of the dose in renal impairment is not warranted.

INDICATIONS
Flomax 0, 4 SR 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.

CONTRAINDICATIONS
Hypersensitivity to tamsulosin hydrochloride, or any other components of Flomax 0.4 SR.
A history of orthostatic hypotension.
Hepatic insufficiency.
Flomax 0,4 SR should not be used in combination with strong inhibitors of CYP3A4, e.g. ketoconazole (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS
A decrease in blood pressure can take place during therapy with Flomax 0,4 SR, as a result of which orthostatic hypotension and 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 Flomax 0,4 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.

The “Intraoperative Floppy Iris Syndrome” (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients previously treated with Flomax 0,4 SR. IFIS may increase the risk of eye complications during and after the operation. Discontinuing Flomax 0,4 SR 1 to 2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not yet been established. IFIS has also been reported in patients who had discontinued Flomax 0,4 SR for a longer period prior to eye surgery.

The initiation of therapy with Flomax 0,4 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 Flomax 0,4 SR in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

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

Flomax 0,4 SR should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (see Interactions).

Flomax 0,4 SR is intended for adult male patients only.

Effects on ability to drive and use machines
No data is available on whether Flomax 0,4 SR adversely affects the ability to drive or operate machinery. However, in this respect, patients should be aware of the fact that dizziness may occur.

INTERACTIONS
No interactions have been seen when Flomax 0,4 SR was given concomitantly with either atenolol, enalapril, or theophylline.

Concomitant cimetidine brings about a rise in plasma levels of tamsulosin and concomitant furosemide brings about a fall, but as levels remain within the normal range dosages need not be changed.

Diazepam, propanolol, trichlormethazide, chlormadinone, 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, propanolol, trichlormethiazide and chlormadinone.

Diclofenac and warfarin, may increase the elimination rate of tamsulosin.

Concomitant administration of Flomax 0,4 SR 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 C_{max} of tamsulosin hydrochloride by a factor of 2.8 and 2.2, respectively. Since CYP2D6 poor metabolisers cannot be readily identified and the potential for significant increase in tamsulosin hydrochloride exposure exists when Flomax 0,4 SR is co-administered with strong CYP3A4 inhibitors in CYP2D6 poor metabolisers, Flomax 0,4 SR should not be given in combination with strong inhibitors of CYP3A4 (see Contraindications). Flomax 0,4 SR should be given with caution in combination with moderate inhibitors of CYP3A4.

Concomitant administration of Flomax 0,4 SR with paroxetine, a strong inhibitor of CYP2D6, resulted in a C_{max} and AUC of tamsulosin that 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.

HUMAN REPRODUCTION
Flomax 0,4 SR is not indicated for use in women.
Fertility
Ejaculation disorders have been observed in short and longterm clinical studies with tamsulosin. Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported post-marketing.

DOSAGE AND DIRECTIONS FOR USE
One capsule daily to be taken after breakfast or the first meal of the day.
The capsule should be swallowed whole and must not be crunched or chewed, as this will interfere with the sustained release property 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 Contraindications).
Paediatric population
There is no indication for use of Flomax 0,4 SR in children.
The safety and efficacy of tamsulosin in children <18 years have not been established.

SIDE-EFFECTS
The following medicine related side-effects have been reported during the use of Flomax 0,4 SR:
Common: ≥1/100, <1/10 Uncommon: ≥1/1000, <1/100 Rare: ≥1/10 000,<1/1000
Very rare: <1/10,000

Nervous system disorders
Common: Dizziness
Uncommon: Headache
Rare: Syncope
Cardiac disorders
Uncommon: Palpitations
Vascular disorders
Uncommon: Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis
Gastrointestinal disorders

Uncommon: Constipation, diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, urticaria
Rare: Angioedema
Very rare: Stevens-Johnson Syndrome
Reproductive system disorders
Common: Ejaculation disorders including retrograde ejaculation and ejaculation failure
Very Rare: Priapism
General disorders and administrative site conditions
Uncommon: Aesthenia

Post-marketing experience (Frequency unknown):

Eye Disorders:	Blurred vision, visual impairment
Respiratory, thoracic and mediastinal disorders:	Epistaxis
Skin and subcutaneous tissue disorders	Erythema multiforme, exfoliative dermatitis

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Symptoms
Overdosage with Flomax 0,4 SR may result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing. The highest dose of Flomax 0,4 SR accidentally given to a single patient was 12 mg, resulting in headache but not requiring hospitalization.
Treatment
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, activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

IDENTIFICATION
Flomax 0,4 SR is a capsule with an orange body and an olive green cap with the Astellas logo, “0,4” and “701” printed in black on the capsule.

PRESENTATION
Three blister strips of 10 capsules

STORAGE INSTRUCTIONS
Store below 25 °C. Protect from moisture.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
South Africa: 30/34/0428
Namibia: Reg. No. 06/34/0043
Kenya: CTD2117
Botswana: BOT0200514

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Astellas Pharma (Pty) Ltd, 7 Mirage Road, Bedfordview 2007, South Africa

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