PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PRAVLEX SR 0,4 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **PRAVLEX SR 0,4 mg** sustained release capsule contains 0,4 mg tamsulosin hydrochloride.

Sugar free

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Sustained release capsule

PRAVLEX SR 0,4 mg

Olive green opaque/ orange opaque, size 2, hard gelatin capsules containing free flowing white to off white spheroids with "CL 23" on cap and "0.4" on the body imprinted with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRAVLEX 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

Posology:

Adults:

One capsule daily.

Special populations

No dose adjustment is warranted in renal impairment.

No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see section 4.3).

Paediatric population

There is no indication for use of **PRAVLEX** in children.

The safety and efficacy of tamsulosin in children <18 years have not been established.

Method of administration

PRAVLEX is administered orally 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.

4.3 Contraindications

PRAVLEX is contraindicated in patients with:

- Hypersensitivity to tamsulosin hydrochloride, or any other components of **PRAVLEX** (see section 6.1).
- A history of orthostatic hypotension.
- Hepatic insufficiency.
- **PRAVLEX** should not be used in combination with strong inhibitors of CYP3A4, e.g. ketoconazole.

4.4 Special warnings and precautions for use

A decrease in blood pressure can take place during therapy with **PRAVLEX**, 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 **PRAVLEX** 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 tamsulosin. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin 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 tamsulosin for a longer period prior to eye surgery.

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

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

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

PRAVLEX 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 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 **PRAVLEX** 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 **PRAVLEX** is co-administered with strong CYP3A4 inhibitors in CYP2D6 poor metabolisers, **PRAVLEX** should not be given in combination with strong inhibitors of CYP3A4 (see section 4.3). **PRAVLEX** should be given with caution in combination with moderate inhibitors of CYP3A4.

Concomitant administration of tamsulosin 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 alpha1-adrenoceptor antagonists could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

PRAVLEX is not indicated for use in women.

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 post-marketing.

4.7 Effects on ability to drive and use machines

No data is available on whether **PRAVLEX** adversely affects the ability to drive or operate machinery. However, in this respect, patients should be aware of the fact that dizziness, drowsiness, blurred vision and syncope may occur.

4.8 Undesirable effects

Tabulated summary of adverse events

System organ class	**Frequency**	**Undesirable effect**

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	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, pruritis, urticaria, angioedema, Stevens-Johnson syndrome
	Frequency unknown	Erythema multiforma, dermatitis exfoliative
Reproductive systems and breast disorders	Frequent	Ejaculation disorders, including retrograde ejaculation and ejaculation failure
	Less frequent	Priapism
General disorders and administration site conditions	Less frequent	Asthenia

Drowsiness or oedema can occur.

During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of tamsulosin during post-marketing surveillance (see also Section 4.4).

In addition to the adverse events listed above, atrial fibrillation, dysrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use. Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of tamsulosin in their causation cannot be estimated from the available data.

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

Overdosage with **PRAVLEX** may result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

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.

5. PHARMACOLOGICAL PROPERTIES

Category and Class: A.34 Other

Pharmacotherapeutic group: Alpha1-adrenoceptor antagonist.

ATC code: G04CA02

5.1 Pharmacodynamic properties

Mechanism of action:

Tamsulosin binds selectively and competitively to postsynaptic alpha1-receptors, in particular to the subtype $alpha_{1A}$, and $alpha_{1D}$ which bring about relaxation of the smooth muscle of the prostate, whereby tension is reduced.

5.2 Pharmacokinetic properties

Absorption

Tamsulosin hydrochloride is absorbed from the intestine and is almost completely bioavailable.

Absorption of tamsulosin hydrochloride is reduced by a recent meal.

Uniformity of absorption can be improved by the patient always taking **PRAVLEX** after the same meal each day.

Tamsulosin shows linear kinetics.

After a single dose of tamsulosin 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 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 drug metabolising enzymes may lead to increased exposure to tamsulosin hydrochloride (see Sections 4.4 and 4.5).

No dose adjustment is warranted in hepatic insufficiency.

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

Elimination

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

After a single dose of tamsulosin in the fed state, and in the steady state in patients, elimination half-lives of about 10 and 13 hours respectively have been measured.

The presence of renal impairment does not warrant lowering the dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate, methacrylic acid copolymer, microcrystalline cellulose, Polysorbate 80, sodium lauryl sulfate, triacetin.

Capsule shell: gelatin, FD & C Blue 2 (C.I. 73015), Iron oxide black (C.I. 77499), Iron oxide red (C.I. 77491), Iron oxide yellow (C.I.77492) and titanium dioxide (C.I. 77891), sodium lauryl sulfate.

Capsule body: gelatin, Iron oxide red (C.I. 77491), Iron oxide yellow (C.I.77492) and titanium dioxide (C.I. 77891) and sodium lauryl sulfate.

Hard gelatin capsule contains black edible printing ink.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack:

36 months from date of manufacture

HDPE container pack

24 months from date of manufacture

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the blisters in the carton until required for use

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack:

Capsules are packed in Clear Film PVC/PE/PVdC, 250 µ /25 µ/90 GSM as forming material and Plain silver coloured aluminum foil, 25 µ, 6-8 GSM as the lidding material.

Pack size: 30's

HDPE Container Pack:

Capsules are packed in 30 cc, round white HDPE bottle with 28-400 neck finish closed with a white 28 mm child resistant closure with pulp and heat seal liner.

Pack size: 30's

Not all packs and pack size are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

48/34/0855

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2022

10. DATE OF REVISION OF THE TEXT

To be advised.