MODULE 1.3.1.1: APPROVED PACKAGE INSERT FOR

UROMAX (MODIFIED RELEASE CAPSULES)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

UROMAX (Modified release capsules)

COMPOSITION:

Each capsule contains 0,4 mg tamsulosin hydrochloride equivalent to 0,367 mg tamsulosin in a modified release pellet formulation.

The inactive ingredients are colloidal anhydrous silica, Eudragit L30 D-55, hypromellose (HPMC E-15 and HPMC 6 cps), polysorbate 80, propylene glycol, purified talc, sugar spheres, Surelease E-7-7050, triethyl citrate and hard gelatine capsules.
Contains sugar (sucrose).

PHARMACOLOGICAL CLASSIFICATION:

A. 18.10 Other.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Tamsulosin binds selectively and competitively to the postsynaptic alpha$_1$-adrenoceptors with greatest affinity for the subtype alpha$_{1A}$ and 1D. Binding of tamsulosin to its receptor induces relaxation of smooth muscle in the bladder neck and prostate, which results in an improvement in urinary flow rate.

It improves the storage symptoms in which bladder instability plays an important role. During long-term therapy these effects on storage and voiding symptoms are maintained, thereby significantly delaying the need for surgery or catheterisation.

Alpha$_1$-antagonists also cause a reduction in 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 with almost 100 % bioavailability. Absorption of tamsulosin is reduced if taken shortly after a meal. Uniformity of absorption can be improved by taking tamsulosin after breakfast.

It takes approximately 6 hours for peak plasma levels to be reached if a single dose of tamsulosin is taken after a meal.

After multiple dosing steady state is reached by day 5. Maximum plasma concentration (C_{max}) in steady state is approximately two-thirds higher with multiple dosing than that achieved after a single dose. Although these results were seen in elderly patients, it is expected that younger patients will show similar results.

Considerable inter-patient variation in plasma levels are observed after both single and multiple dosing.

Distribution:

Tamsulosin is approximately 99 % bound to plasma proteins and has a small volume of distribution (about 0,21 ℓ/kg).

Metabolism:

Since tamsulosin is metabolised slowly, it has a low first pass effect. In plasma, tamsulosin is mostly present in the form of the unchanged medicine. Metabolism occurs in the liver.

Tamsulosin caused induction of microsomal liver enzymes in animal studies. CYP3A4 and CYP2D6 are however involved in tamsulosin hydrochloride metabolism *in vitro*, with possible minor contributions by other CYP isozymes. CYP3A4 and CYP2D6 enzyme inhibition may lead to increased tamsulosin hydrochloride exposure (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).

None of the metabolites exhibit greater activity than the parent compound.

Elimination:

Tamsulosin and its metabolites are mainly excreted in the urine. Approximately 9 % of a dose is present in the urine as unchanged medicine. While the elimination half-life after a single dose is approximately 10 hours, this increases to approximately 13 hours during steady state.

INDICATIONS:

UROMAX is indicated to relieve functional symptoms of benign prostatic hyperplasia (BPH).

CONTRAINDICATIONS:

UROMAX is contraindicated in:

- Patients hypersensitive to tamsulosin hydrochloride or any other components of **UROMAX**.
- Patients with a history of orthostatic hypotension.
- Patients with severe hepatic insufficiency.
- Combination with strong inhibitors of CYP3A4, e.g. ketoconazole (see **"INTERACTIONS"**).
- Females, children and breastfeeding women.

WARNINGS AND SPECIAL PRECAUTIONS:

UROMAX is intended for use in males only.

Treatment with **UROMAX** may cause a decrease in blood pressure followed by orthostatic hypotension and syncope. If ever patients should experience the first signs of orthostatic hypotension, namely dizziness and weakness, they should sit or lie down until the symptoms have disappeared.

Prior to initiation of therapy with **UROMAX**, patients should be examined to exclude other conditions that may present with similar symptoms as benign prostatic hyperplasia. Digital

rectal examination, and if indicated, determination of prostate specific antigen (PSA) should be performed prior to treatment and at regular intervals thereafter.

Since patients with severe renal impairment (creatinine clearance < 10 mℓ/min) have not been studied they should be treated with caution.

Some patients on or previously treated with tamsulosin, as in **UROMAX**, developed 'Intraoperative Floppy Iris Syndrome' (IFIS – a variant of small pupil syndrome) during cataract and glaucoma surgery. IFIS is associated with an increased risk for the development of procedural complications during cataract and glaucoma operations.
Treatment with **UROMAX** should not be initiated in patients scheduled for cataract or glaucoma surgery.
Although anecdotal reports suggest that tamsulosin therapy should be discontinued 1 – 2 weeks prior to cataract or glaucoma surgery, the benefit and duration of interruption of therapy prior to surgery has not yet been established. In patients who had stopped **UROMAX** for longer than 2 weeks before surgery, IFIS has also been reported. Surgeons and ophthalmic teams should give proper consideration to the possibility of current or previous treatment with tamsulosin during the preoperative assessment of patients scheduled for cataract or glaucoma surgery to ensure that appropriate measures will be in place to manage IFIS during surgery.

Ejaculation disorders have been observed with short-term and long-term use of **UROMAX**. Ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported.

Effects on ability to drive and use machines:

Dizziness, drowsiness, blurred vision and syncope, which may negatively impact on an individual's ability to drive and operate machinery, may occur.

Sucrose:

UROMAX contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take **UROMAX.**

INTERACTIONS:

No interactions have been observed when **UROMAX** was co-administered with atenolol, enalapril, nifedipine or theophylline. Co-administration with cimetidine causes increases in plasma levels of tamsulosin, while concomitant furosemide administration gives rise to decreased plasma levels of tamsulosin. Since plasma levels remain within the normal range posology need not be changed.

According to results obtained *in vitro*, diazepam, propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin do not

change the free fraction of tamsulosin in human plasma. Neither does tamsulosin cause changes in the free fractions of diazepam, propranolol, trichlormethiazide and chlormadinone.

Diclofenac and warfarin may cause an increase in the elimination rate of tamsulosin.

In vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolising enzyme system) did not demonstrate any interactions at the level of hepatic metabolism involving amitriptyline, salbutamol, glibenclamide and finasteride.

Co-administration of **UROMAX** with strong inhibitors of CYP3A4 may cause increased tamsulosin hydrochloride exposure. Co-administration with ketoconazole (a known strong CYP3A4 inhibitor) results in an increase in tamsulosin hydrochloride AUC and C_{max} by a factor of 2,8 and 2,2, respectively.

UROMAX should not be given in combination with strong inhibitors of CYP3A4, since CYP2D6 poor metabolisers cannot be easily identified and the possibility of significant increase in tamsulosin hydrochloride exposure exists when **UROMAX** is used concomitantly with strong CYP3A4 inhibitors in CYP2D6 poor metabolisers (see **"CONTRAINDICATIONS"**).

UROMAX should be administered with care in combination with moderate inhibitors of CYP3A4, e.g. erythromycin.

Co-administration of **UROMAX** with paroxetine, a strong inhibitor of CYP2D6, causes an increase in tamsulosin C_{max} and AUC by a factor of 1,3 and 1,6, respectively; however, these increases are not considered clinically relevant.

Co-administration of other alpha$_1$-adrenoceptor blockers may exacerbate tamsulosin's hypotensive effects.

PREGNANCY AND LACTATION:

UROMAX is not indicated for use in females (see "**CONTRAINDICATIONS**").

DOSAGE AND DIRECTIONS FOR USE:

One 0,4 mg **UROMAX** capsule is to be taken daily after breakfast.

The modified release formulation of **UROMAX** should be swallowed whole with water (about 150 mℓ) in the standing or sitting position.

To avoid interference with the modified release property of the active ingredient, the modified release formulation of **UROMAX** should not be crunched or chewed.

Dosage adjustment is not required in patients with mild to moderate renal impairment (see also "**WARNINGS AND SPECIAL PRECAUTIONS**).

Dosage adjustment is not required in patients with mild to moderate hepatic insufficiency (see also **"CONTRAINDICATIONS"**).

SIDE-EFFECTS:

The following side-effects have been reported during use of **UROMAX**:

Immune system disorders:

Less frequent: Hypersensitivity reactions such as rash, pruritus and urticaria, and angioedema, Stevens-Johnson syndrome.

Nervous system disorders:

Frequent: Dizziness.

Less frequent: Headache, syncope.

Frequency unknown: Drowsiness.

Eye disorders:

Frequency unknown: Intraoperative Floppy Iris Syndrome (IFIS) (see **"WARNINGS AND SPECIAL PRECAUTIONS"**), blurred vision, visual impairment.

Cardiac disorders:

Less frequent: Palpitations.

Frequency unknown: Atrial fibrillation, dysrhythmia, tachycardia.

Vascular disorders:

Less frequent: Orthostatic (postural) hypotension.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Rhinitis.

Frequency unknown: Epistaxis, dyspnoea.

Gastrointestinal disorders:

Less frequent: Constipation, nausea, vomiting, diarrhoea.

Frequency unknown: Dry mouth.

Skin and subcutaneous tissue disorders:

Less frequent: Rash, pruritus, urticaria.

Frequency unknown: Erythema multiforme, exfoliative dermatitis.

Reproductive system and breast disorders:

Frequent: Abnormal ejaculation, including retrograde ejaculation and ejaculation failure.

Less frequent: Priapism.

General disorders and administrative site conditions:

Less frequent: Asthenia.

Frequency unknown: Oedema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may induce acute hypotension in which case cardiovascular support should be given. Blood pressure and heart rate may be normalised by lying the patient down.

Should this fail to restore blood pressure and heart rate to normal, volume expanders and, when necessary, vasopressors could be used.

It is important to monitor renal function and to apply general supportive measures.

Since tamsulosin is highly protein-bound, it is unlikely that dialysis will be of help.

Emesis may be induced to impede absorption. Gastric lavage followed by the administration of activated charcoal and an osmotic laxative, such as sodium sulphate, may be appropriate if large quantities are involved.

IDENTIFICATION:

White to off-white pellets filled in size “2” hard gelatine capsules with brown cap and off-white opaque body.

PRESENTATION:

PVC/PVDC/Aluminium foil blister strips of 10 capsules packed in 30’s.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Protect from excessive heat, freezing and moisture.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/34/0046

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD.

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