SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cositam XL 400 microgram prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 400 microgram tamsulosin hydrochloride, equivalent to 367 microgram tamsulosin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, unscored, round tablets with a diameter of 9 mm, debossed on one side with "T9SL" and “0.4” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Oral use.

One tablet daily.

Tamsulosin can be taken independently of food.

The tablet must be swallowed whole and not be crunched or chewed as this interferes with the prolonged release of the active substance.

No dose adjustment is warranted in renal impairment.

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

Paediatric population
The safety and efficacy of tamsulosin in children and adolescents have not been established. Currently available data are described in section 5.1.

There is no relevant indication for use of tamsulosin in children.

4.3 Contraindications

- Hypersensitivity to tamsulosin hydrochloride, including drug-induced angioedema or to any of the excipients.
- A history of orthostatic hypotension.
- Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin, as a result of which, rarely, 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 tamsulosin 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 surgery in some patients on or previously treated with tamsulosin. IFIS may lead to increased procedural complications during the operation. The initiation of therapy with tamsulosin in patients for whom cataract surgery is scheduled is not recommended.

Discontinuing tamsulosin 1-2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration 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 in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

It is possible that a remnant of the tablet is observed in the faeces.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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, whereas furosemide a fall, but as levels remain within the normal range posology need not be adjusted.

In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free

fractions of diazepam, propranolol, trichlormethiazide and chlormadinone.

No interactions at the level of hepatic metabolism have been seen 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 theelimination rate of tamsulosin.

Concurrent administration of other α1-adrenoceptor antagonists could lead to hypotensive effects.

4.6 Fertility, Pregnancy and lactation

Not applicable, as tamsulosin is intended for male patients only.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
However, patients should be aware of the fact that dizziness can occur.

4.8 Undesirable effects

MedDRA system organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Nervous systems disorders	Dizziness (1.3%)	Headache	Syncope	
Cardiac disorders		Palpitations		
Vascular disorders		Orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Rhinitis		

Gastro-intestinal disorders		Constipation, diarrhoea, nausea, vomiting		
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	Angioedema	Stevens-Johnson syndrome
Reproductive system and breast disorders	Ejaculation disorders			Priapism
General disorders and administration site conditions		Asthenia		

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

Post-marketing experience: In addition to the adverse events listed above, atrial fibrillation, arrhythmia, 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 reliably determined.

4.9 Overdose

Acute overdose with 5 mg of tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed, which were treated with fluid replacement and the patient could be discharged the same day.

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, 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

Pharmacotherapeutic group: Drugs used in benign prostatic hypertrophy, Alpha-adrenoreceptor antagonists; ATC code: G04C A02.

Mechanism of action

Tamsulosin binds selectively and competitively to the postsynaptic α1-adrenoceptors, in particular to subtypes α1A and α1D. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects

Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra thereby improving voiding symptoms.

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. Observational data indicate that use of tamsulosin may lead to a delay in the need for surgery or catheterization.

α1-adrenoceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

Paediatric population

A double-blind, randomized, placebo-controlled, dose ranging study was performed in children with neuropathic bladder. A total of 161 children were randomized and treated at 1 of 3 dose levels of tamsulosin (low [0.001 to 0.002 mg/kg], medium [0.002 to 0.004 mg/kg], and high [0.004 to 0.008 mg/kg]), or placebo. A response was defined as a primary endpoint with patients who decrease their detrusor leak

point pressure (LPP) to <40 cm H2O based upon two evaluations on the same day. Secondary endpoint were: Actual and percent change from baseline in detrusor leak point pressure, improvement or stabilization of hydronephrosis and hydroureter and change in urine volumes obtained by catheterisation and number of times wet at time of catheterisation as recorded in catheterisation diaries. No statistically significant differences were found between the placebo group and any of the 3 tamsulosin dose groups for either the primary or any secondary endpoint. Additional exploratory analyses in subgroups confirmed these findings (e.g. age, anti-cholinergic use, weight, geographic regions). No dose response was observed for any dose level.

5.2 Pharmacokinetic properties

Absorption
The Tamsulosin prolonged-release formulation provides consistent slow release oftamsulosin, resulting in an adequate exposure, with little fluctuation, over 24 hours.

Tamsulosin administered as Tamsulosin prolonged-release tablets is absorbed from the intestine. Of the administered dose, approximately 57% is estimated to be absorbed.

The rate and extent of absorption of tamsulosin administered as Tamsulosin hydrochloride prolonged release tablets are not affected by food.

Tamsulosin shows linear pharmacokinetics.

After a single dose of tamsulosin in the fasted state, plasma concentrations of tamsulosin peak at a median time of 6 hours. In steady state, which is reached by day 4 of multiple dosing, plasma concentrations of tamsulosin peak at 4 to 6 hours, in the fasted and fed state. Peak plasma concentrations increase from approximately 6 ng/ml after the first dose to 11 ng/ml in steady state.
As a result of the prolonged-release characteristics of Tamsulosin prolonged-release tablets the trough concentration of tamsulosin in plasma amounts to 40% of the peak plasma concentration under fasted and fed conditions.

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. The 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 active substance. It is metabolised in the liver.

In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.

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

Elimination

Tamsulosin and its metabolites are mainly excreted in the urine. The amount excreted as unchanged active substance is estimated to be about 4 - 6% of the dose, administered as Tamsulosin prolonged-release tablets.

After a single dose of tamsulosin and in steady state, elimination half-lives of about 19 and 15 hours, respectively, have been measured.

5.3 Preclinical safety data

Single and repeat dose toxicity studies were performed in mice, rats and dogs. In addition, reproduction toxicity in rats, carcinogenicity in mice and rats and in vivo and in vitro genotoxicity were examined.

The general toxicity profile, as seen with high doses of tamsulosin, is consistent with the known pharmacological actions of the α-adrenoceptor antagonists.

At very high dose levels the ECG was altered in dogs. This response is considered to be not clinically relevant. Tamsulosin showed no relevant genotoxic properties. Increased incidences of proliferative changes of mammary glands of female rats and mice have been reported. These findings, which are probably mediated by hyperprolactinemia and only occurred at high dose levels, are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

• *Inner core tablet:*
• Hypromellose
• Microcrystalline cellulose
• Carbomer
• Colloidal anhydrous silica
• Iron oxide red (E172)
• Magnesium stearate

• *Outer tablet:*
• Microcrystalline cellulose
• Hypromellose
• Carbomer
• Colloidal anhydrous silica
• Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package to protect from light.

6.5 Nature and contents of container

PVC/PVDC:Al blister packs containing 10, 18, 20, 28, 30, 50, 60, 90, 98 and 100 tablets.

PVC/Aclar:Al blíster packs containing 10, 18, 20, 28, 30, 50, 60, 90, 98 and 100 tablets

oPA/Al/PVC/Al blíster packs containing 10, 18, 20, 28, 30, 50, 60, 90, 98 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Firstline Pharma Ltd.
Ravalco House, Cleveland Way,
Hemel Hempstead,
Hertfordshire, HP2 7DL,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 42177/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/12/2010 / 31/03/2015

10 DATE OF REVISION OF THE TEXT

12/02/2024