

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prolosin 400 microgram prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release capsule contains 400 micrograms tamsulosin hydrochloride

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule.

Capsule filled with white or off-white pellets

Capsule shell size no. 2, standard brown opaque C015 cap and buff opaque C0006 body.

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

One capsule daily, to be taken after breakfast or the first meal of the day.

The capsule should be swallowed whole and should not be crunched or chewed as this will interfere 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 Section 4.3, Contraindications).

Paediatric population

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

The safety and efficacy of tamsulosin in children <18 years have not been established. Currently available data are described in section 5.1

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 α_1 -adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Prolosin 400 microgram prolonged release capsules, 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 Prolosin 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 $<10\text{ml/min}$) 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 increase the risk of eye complications during and after 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 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 in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (section 4.5).

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 Prolosin was given concomitantly with either atenolol, enalapril, nifedipine or theophylline.

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

In vitro neither diazepam nor propranolol, trichlormethiazide, chlormadinon, 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 chlormadinon.

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

Concomitant administration of tamsulosin hydrochloride 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. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.

Concomitant administration of tamsulosin hydrochloride 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 α_1 -adrenoceptor antagonists could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

Prolosin is not indicated for use in women.

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 authorization phase.

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

	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10000, <1/1000)	Very rare (<1/10000)	Not known (cannot be estimated from available data)
Nervous system disorders	Dizziness (1.3%)	Headache	Syncope		
Cardiac disorders		Palpitations			
Vascular disorders		Orthostatic hypotension			
Respiratory, thoracic and mediastinal disorders		Rhinitis			Epistaxis
Gastrointestinal disorders		Constipation, diarrhoea, nausea, vomiting			
Skin and		Rash,	Angio-	Stevens-	Erythema

subcutaneous tissue disorders		pruritis, urticaria	oedema	Johnson syndrome	multiforme, Dermatitis exfoliative
Reproductive systems and breast disorders	Ejaculation disorders	Abnormal ejaculation		Priapism	Ejaculation disorder, retrograde ejaculation, ejaculation failure
General disorders and administration site conditions		Asthenia			
Eye disorders					Vision blurred, vision impairment

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 also 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 readily determined.

As with other alpha-blockers, drowsiness, blurred vision, dry mouth or oedema can occur.

4.9 Overdose

Symptoms

Overdosage with tamsulosin hydrochloride can potentially 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, 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:

Alpha₁-adrenoceptor antagonist.

ATC code: G04C A02. Preparations for the exclusive treatment of prostatic disease.

Mechanism of action:

Tamsulosin binds selectively and competitively to the postsynaptic alpha₁-receptors, in particular to the subtypes alpha_{1A} and alpha_{1D}. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects:

Prolosin 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. The need for surgery or catheterisation is significantly delayed.

Alpha₁-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Prolosin.

Paediatric population

A double-blind, randomized, placebo-controlled, dose ranging study was performed in children with neuropathic bladder. A total of 161 children (with an age of 2 to 16 years) 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. The primary endpoint was number of patients who decreased their detrusor leak point pressure (LPP) to <40 cm H₂O based upon two evaluations on the same day. Secondary endpoints 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 difference was found between the placebo group and any of the 3 tamsulosin dose groups for either the primary or any secondary endpoints. No dose response was observed for any dose level.

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 promoted by the patient always taking Prolosin after the same meal.

Tamsulosin shows linear kinetics.

After a single dose of Prolosin 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 drug. It is metabolised in the liver.

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

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

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

After a single dose of Prolosin in the fed state, and in the steady state in patients, elimination half-lives of about 10 and 13 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 studies 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 alpha-adrenergic blocking agents.

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 hyperprolactinaemia and only occurred at high dose levels are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Calcium stearate
Triethyl citrate
Talc
Methacrylic acid-ethyl acrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Microcrystalline cellulose

Capsule (upper part)

Yellow iron oxide (E172)
Titanium dioxide (E171)
Black iron oxide (E172)
Red iron oxide (E172)
Gelatin

Capsule (lower part)

Red iron oxide (E172)
Black iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

The capsules are available in Al/PVC/PVdC blister packs of 30.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited
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Wilbury Way
Hitchin
Herts SG4 OTW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1063/21/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 17th February 2011

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