

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pamsvax XL 400micrograms capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule, hard contains 400 micrograms tamsulosin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

330mg white or off-white film-coated pellets are filled in the size No. 2 capsules which upper part is brown opaque, lower part is buff opaque.

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

Posology

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

Paediatric population

There is no relevant indication for use of Pamsvax XL 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.

Use in renal impairment

No dosage adjustment is warranted in patients in renal impairment.

Use in hepatic impairment

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

Method of administration

For oral use. The capsule should be swallowed whole and should not be crunched or chewed as this will interfere with the prolonged release of the active ingredient.

4.3 Contraindications

- Hypersensitivity to the active substance, including drug-induced angioedema, or to any of the excipients listed in section 6.1.
- 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 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 or glaucoma surgery in some patients on or

previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation.

Discontinuing tamsulosin 1-2 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 cataract surgery.

The initiation of therapy with tamsulosin in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma 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 (see section 4.5).

This medicine contains less than 1 mmol sodium (23 mg) per prolonged-release capsule, hard, that is to say essentially 'sodium-free'.

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.

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.

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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

Tamsulosin is not indicated for use in women.

Ejaculation disorders have been observed in short and long term clinical studies in men. Events of retrograde ejaculation and ejaculation failure have been reported in the post authorisation 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

<i>System Organ Class</i>	<i>Common ($\geq 1/100$ to <1/10)</i>	<i>Uncommon ($\geq 1/1,000$ to <1/100)</i>	<i>Rare ($\geq 1/10,000$ to <1/1,000)</i>	<i>Very rare (<1/10,000)</i>	<i>Not known (the frequency cannot be estimated from the available data)</i>
Nervous system disorders	Dizziness (1.3%)	Headache	Syncope		
Eye disorders					Vision blurred*, Visual impairment*
Cardiac		Palpitations			

disorders					
Vascular disorders		Orthostatic hypotension			
Respiratory, thoracic and mediastinal disorders		Rhinitis			Epistaxis*
Gastrointestinal disorders		Constipation, Diarrhoea, Nausea, Vomiting			Dry mouth*
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	Angioedema	Stevens-Johnson syndrome	Erythema multiforme*, Dermatitis exfoliative*
Reproductive system and breast disorders	Ejaculation disorders, Retrograde ejaculation, Ejaculation failure			Priapism	
General disorders and administration site conditions		Asthenia			

*Post-marketing experience

During cataract or 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Overdose with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

The highest dose ingested following unintentional overdose of tamsulosin hydrochloride was 12mg. This resulted in severe headache. No hospitalisation was needed.

Treatment

In case of acute hypotension occurring after overdose 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 sulfate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Alpha-adrenoreceptor antagonists, ATC code: G04C A02

Preparations for the exclusive treatment of prostatic disease.

Mechanism of action

Tamsulosin binds selectively and competitively to the postsynaptic $\alpha 1$ -adrenoceptors, in particular to subtypes $\alpha 1A$ and $\alpha 1D$. 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. The need for surgery or catheterisation is significantly delayed.

$\alpha 1$ -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 (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 tamsulosin after the same meal. 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. 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. 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 metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride (see section 4.4 and 4.5). 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 drug. 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.

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_1 -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 hyperprolactinaemia and only occurred at high dose levels are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Microcrystalline cellulose (E460),
Methacrylic acid - ethyl acrylate copolymer 1:1 (including: polysorbate 80,
sodium laurilsulfate),
Talc,
Triethyl citrate,
Calcium stearate.

Capsule shell:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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

10, 20, 30, 50, 90 or 100 capsules are packed into colourless, transparent PVC/PVDC/Aluminium blisters.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/1224

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

Date of first authorisation: 26 January 2006
Date of latest renewal: 14 January 2015

10 DATE OF REVISION OF THE TEXT

07/05/2021