SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TAMFREX XL 400 microgram capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule, hard contains 0.4 mg of tamsulosin hydrochloride.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Olive green opaque/ Orange opaque size '1EL' hard gelatin capsules imprinted with 'D' on cap and '53' on body with black edible ink filled with white to off-white beadlets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tamsulosin is indicated in adults for the treatment of functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology

One capsule daily, to be taken with or without food.

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 < 18 years have not been established. Currently available data are described in section 5.1.

Method of administration

For oral use.

The capsule should be swallowed whole and should not be crunched or chewed as this interferes with the prolonged release of the active ingredient.

4.3 Contraindications

Hypersensitivity to tamsulosin hydrochloride, or to any of the excipients listed in section 6.1.

A history of orthostatic hypotension; severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other α_1-blockers, 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 severely renally impaired patients (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 on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation.

Discontinuing tamsulosin hydrochloride 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 the surgery.

The initiation of therapy with tamsulosin hydrochloride 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 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 (e.g. ketoconazole) in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong (e.g. ketoconazole) and moderate (e.g. erythromycin) inhibitors of CYP3A4 (see section 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with 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 changed.

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 Cmax 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 (e.g. ketoconazole) and moderate inhibitors (e.g. erythromycin) of CYP3A4.

Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a Cmax 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.

There is a theoretical risk of enhanced hypotensive effect when given concurrently with other drugs which may reduce blood pressure , including anaesthetic agents and other α 1-adrenoceptor antagonists..

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 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 drowsiness, blurred vision, dizziness and syncope can occur.

4.8 Undesirable effects

System Organ Class	Common (>1/100,to <1/10)	Uncommon (>1/1 000, <1/100)	Rare (≥1/10 000, <1/ 1 000)	Very rare (<1/10 000)	Not known (cannot be estimated from the available data)
Nervous system disorders	Dizziness (1.3%)	Headache	Syncope		

Eye disorders					Vision blurred*, Visual impairment*
Cardiac disorders		Palpitations			
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	Angio-oedema	Stevens-Johnson syndrome	Erythema multiforme*, Dermatitis exfoliative*
Reproductive systems and breast disorders	Ejaculation disorders, Retrograde ejaculation, Ejaculation failure			Priapism	
General disorders and administration site conditions		Asthenia			

* Observed post-marketing.

As with other α blockers, drowsiness, blurred vision 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).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects, dizziness and malaise. 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 sulpfate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: α 1-adrenoceptor antagonist, ATC code: GO4C AO2. Preparations for the exclusive treatment of prostatic disease.

Mechanism of action:

Tamsulosin binds selectively and competitively to postsynaptic α 1receptors, in particular to subtypes α 1A,which brings about relaxation of the smooth muscles of the prostatic , whereby tension is reduced.

Pharmacodynamic effects

Tamsulosin increases the maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra,thereby relieving obstruction.

It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary track plays an important role.

α_{1}-blockers 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 formulated as an Oral Controlled Absorption System (OCAS) and is a prolonged release tablet of the non-ionic gel matrix type.

Tamsulosin hydrochloride administered as prolonged release tablets is absorbed from the intestine. Under fasting conditions approximately 57 % of the administered dose is estimated to be absorbed. A consistent slow release of the tamsulosin is maintained over the whole pH range encountered in the gastro-intestinal track with little fluctuation over 24 hours. The extent of absorption is increased by 64% and 149% (AUC and Cmax respectively) by a high fat meal compared to fasted.

After a single dose of Tamsulosin in the fasted state, plasma levels of tamsulosin peak at a median time of 6 hours. In steady state, which is reached by day 4 of multiple dosing, plasma levels of tamsulosin peak at 4 to 6 hours in the fasted and fed state. Peak plasma levels increase from approximately 6ng/ml after the first dose to 11 ng/ml in steady state.

As a result of the prolonged release characteristics of Tamsulosin, 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 more than 99% bound to plasma proteins and the volume of distribution is small (about 0.2 l/kg).

Metabolism

Tamsulosin has a low first pass effect, being metabolized slowly. Most tamsulosin is in plasma in the form of unchanged drug. Itis 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 metablolism by other CYP isozymes. Inhibition of CYP3A4 and CYP2D6 drug metabolizing 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. The amount excreted as unchanged drug is estimated to be about 4-6% of the dose, administered as Tamsulosin. After a single dose of Tamsulosin, and in steady state, elimination half-lives of about 19 hours and 15 hours, respectively, have been measured.

No dose adjustment is necessary in patients with renal impairment.

Linearity/non-linearity
Tamsulosin shows linear kinetics

5.3 Preclinical safety data

Single and repeat dose toxicity studies were performed in rats, carcinogenicity in mice and rats, and *in vivo* genotoxicity were examined.. The general toxicity profile, as seen with high doses of tamsulosin, is consistent with known pharmacological actions of 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 occured at high dose levels , are regarded as irrelevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Content

Cellulose, microcrystalline

Talc

Methacrylic acid-ethyl acrylate copolymer

Sodium lauryl sulfate
Polysorbate 80

Triacetin

Calcium stearate

Capsule shell

Indigo carmine (E132)

Iron oxide red (E172)

Iron oxide yellow (E172)

Titanium dioxide (E171)

Gelatin

Sodium lauryl sulfate

Printing Ink

Shellac

Propylene glycol

Black iron oxide (E172)

Potassium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blister packs

Blister: 1, 2, 4, 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 98, 100 & 200 hard, capsules.

White opaque round HDPE bottle with white opaque polypropylene closure: 10 & 250 hard, capsules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0254

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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