SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tamurex 400 micrograms prolonged-release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 0.4 mg of tamsulosin hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Orange no 2 gelatin capsule which contains white or yellowish granules

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 with or without food.
The capsule should be swallowed whole with a glass of water in sitting or in standing position (not in lying position). The capsule should not be broken or chewed as this will interfere with the modified release of the active ingredient. In cases when patients have difficulties swallowing (e. g. dysphagia), the capsule may be opened and the contents swallowed without chewing.

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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 less than 10 ml/min) should be approached with caution as these patients have not been studied.

Angio-oedema has been rarely reported after the use of tamsulosin. Treatment should be discontinued immediately, patient should be monitored until disappearance of the oedema, and tamsulosin should not be re-administered.

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. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not 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 observed when tamsulosin was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant cimetidine raises, and concomitant furosemide lowers plasma concentrations of tamsulosin but, as the concentration of tamsulosin remains within the normal range, posology need to be altered.

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.

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 (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 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 drugs which may reduce blood pressure, including

anaesthetic agents and other α_1-adrenoceptor antagonists.

No interactions have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked metabolizing enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin may increase the elimination rate of tamsulosin.

4.6 Pregnancy and lactation

Tamsulosin is intended for males only. 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 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, blurred vision, dizziness and syncope can occur.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10,000, <1/1000	Very Rare <1/10,000	Not known (cannot be estimated from the available data)
Nervous system disorders	dizziness (1.3%)	headache	syncope		
Eye disorders	Floppy Iris Syndrome (IFIS, variant of small pupil syndromes during cataract surgery)				Vision blurred* Visual impairmen
Cardiac disorders		Palpitations,			

		Tachycardia			
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, itching, urticaria	angioedema	Stevens-Johnson syndrome	Erythema multiforme Dermatitis exfoliative
Reproductive system and breast disorders	ejaculation disorders including retrograde ejaculation and ejaculation failure			priapism	
General disorders and administration site conditions		asthenia			

*observed post-marketing

As with other alpha-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 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 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: alpha-adrenoreceptor antagonists
ATC code: G04CA02. Preparations for the exclusive treatment of prostatic disease.

Mechanism of action

Tamsulosin binds selectively and competitively to postsynaptic α_{1A} adrenoreceptors, which convey smooth muscle contraction**,** thereby relaxing prostatic and urethral smooth muscle.

Pharmacodynamic effects

Tamsulosin increases the maximum urinary flow rate by relaxing prostatic and urethral smooth muscle, thus relieving obstruction.

The medicinal product also improves the irritative and obstructive symptoms in which the contraction of smooth muscle in the lower urinary tract plays an important role.

Alpha-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin in normotensive patients.

The medicinal product's effect on storage and voiding symptoms are also maintained during long-term therapy, as a result of which the need for surgical treatment is significantly postponed.

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 H_2O 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 is rapidly absorbed from the intestine and its bioavailability is almost complete. Absorption is slowed down if a meal has been eaten before taking the medicinal product. Uniformity of absorption can be assured by always taking tamsulosin after breakfast.

Tamsulosin shows linear kinetics.

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 tamsulosin is maintained over the whole pH range encountered in the gastro-intestinal tract 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.

Peak plasma levels are achieved at approximately six hours after a single dose of tamsulosin taken after a full meal. The steady state is reached by day five of multiple dosing, when Cmax in patients is about two-thirds higher than that reached after a single dose. Although this has been demonstrated only in the elderly, the same result would also be expected in younger patients.

Plasma levels of tamsulosin peak at 4 to 6 hours in the fasted and fed state. Peak plasma levels 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, the trough concentration of tamsulosin in plasma amounts to 40% of the peak plasma concentration under fasted and fed conditions.

There are huge inter-patient variations in plasma levels of tamsulosin, both after single as well as multiple dosing.

Distribution

In man, tamsulosin is about 99% bound to plasma proteins and the volume of distribution is small (about 0.2 l/kg).

Biotransformation

Tamsulosin has a low first pass metabolic effect. Most tamsulosin is found unaltered in plasma in the form of unchanged drug. The substance is metabolised in the liver.

In studies on rats, tamsulosin was found to cause only a slight induction of microsomal liver enzymes.

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).

No dose adjustment is warranted in hepatic insufficiency.

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

The metabolites are not as effective and toxic as the active medicinal product itself.

Excretion

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 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

Toxicity after a single dose and multiple dosing has been investigated in mice, rats and dogs. Reproductive toxicity has also been investigated in rats, carcinogenicity in mice and rats, and genotoxicity *in vivo* and *in vitro*.

The common toxicity profile found with large doses of tamsulosin is equivalent to the pharmacological effect associated with alpha adrenergic antagonists.

Changes in ECG readings were found with very large doses in dogs. This is not, however, assumed to be of any clinical significance. Tamsulosin has not been found to have any significant genotoxic properties.

Greater proliferative changes in the mammary glands of female rats and mice have been discovered on exposure to tamsulosin. These findings, which are probably indirectly linked to hyperprolactinaemia and only occur as a result of large doses having been taken, are considered clinically insignificant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

capsule contents:
sodium alginate
methacrylic acid-ethyl acrylate copolymer 1:1
glycerol dibehenate
maltodextrin
sodium laurilsulphate
macrogol 6000
polysorbate 80
sodium hydroxide
simeticone emulsion (*simeticone, methylcellulose, sorbic acid*)
silica, colloidal anhydrous

capsule shell:
gelatin
red iron oxide (E172)
titanium dioxide (E171)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container.
Do not store above 30°C.

6.5 Nature and contents of container

Blister: PVC/PVDC/Al-blister

Blister are packed in cardboard cartons.

Capsule container: HDPE-container with PP-cap

Pack sizes: 30 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strandhaven Limited T/A Somex Pharma
600 High Road
Seven Kings
Ilford Essex IG3 8BS
United Kingdom
tel: +44 20 8590 9399
fax: +44 20 8599 4437
e-Mail: info@somexpharma.com

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/02/2007

10 DATE OF REVISION OF THE TEXT

31/07/2018