SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flomaxtra® XL, 400 micrograms, film-coated prolonged release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains as active ingredient tamsulosin hydrochloride 400 micrograms, equivalent to 367 micrograms tamsulosin.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated, prolonged release tablet.

Approximately 9 mm, round, bi-convex, yellow, film-coated tablets debossed with the code ‘04’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology

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

Method of administration

For oral use.
The tablet 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

A history of orthostatic hypotension; severe hepatic insufficiency.

Hypersensitivity to tamsulosin hydrochloride or any other component of the product.

4.4 Special warnings and precautions for use

As with other alpha$_1$ blockers, a reduction in blood pressure can occur in individual cases during treatment with Flomaxtra XL, 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 Flomaxtra XL 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.

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 of 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

No interactions at the level of hepatic metabolism have been seen during *in vitro* studies with liver microsomal fractions (representative of the cytochrome P_{450}-linked drug metabolising enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

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.

4.6 Pregnancy and lactation

Not applicable, as Flomaxtra XL is intended for male patients only.

4.7 Effects on ability to drive and use machines

No data is available on whether Flomaxtra XL adversely affects the ability to drive or operate machines. However, in this respect patients should be aware of the fact that drowsiness, blurred vision, dizziness and syncope can occur.

4.8 Undesirable effects

Flomaxtra XL was evaluated in two double - blind placebo controlled trials. Adverse events were mostly mild and their incidence was generally low. The most commonly reported ADR was abnormal ejaculation occurring in approximately 2% of patients.

Suspected adverse reactions reported with Flomaxtra XL or an alternative formulation of tamsulosin, were:-

Nervous systems disorders

Common: dizziness, headache

Uncommon: syncope

Cardiac disorders

Uncommon: palpitations

Vascular disorders

Uncommon: postural hypotension

Respiratory disorders

Uncommon: rhinitis

Gastrointestinal disorders

Uncommon: nausea, vomiting, constipation, diarrhoea

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, urticaria
Very rare: angioedema

Reproductive system disorders

Common: abnormal ejaculation

Very rare: priapism

General disorders
Common: asthenia

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

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).

4.9 Overdose

Acute overdose with 5 mg 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 was able to be discharged the same day. 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 sulphate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Alpha$_1$-adrenoceptor antagonist.

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

Mechanism of action:

Tamsulosin binds selectively and competitively to postsynaptic alpha$_1$-receptors, in particular to the subtype alpha$_{1A}$, which bring about relaxation of the smooth muscle of the prostate, whereby tension is reduced.

Pharmacodynamic effects:

Flomaxtra XL increases 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 tract play an important role. Alpha$_1$-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Flomaxtra XL.

5.2 Pharmacokinetic properties

Absorption:

Flomaxtra XL is formulated as an Oral Controlled Absorption System (OCAS) and is a prolonged release tablet of the non-ionic gel matrix type.

Tamsulosin administered as Flomaxtra XL is absorbed from the intestine and is approximately 55 - 59% bioavailable. 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 rate and extent of absorption of tamsulosin administered as Flomaxtra XL is not affected by food.

Tamsulosin shows linear kinetics.

After a single dose of Flomaxtra 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 6 ng/ml after the first dose to 11 ng/ml in steady state.

As a result of the prolonged release characteristics of Flomaxtra XL, 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 and volume of distribution is small (about 0.2l/kg).

Metabolism:

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 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 Flomaxtra XL.

After a single dose of Flomaxtra XL, 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.

5.3 Preclinical safety data

Single and repeat dose toxicity studies were performed in mice, rats and dogs. In addition, reproduction toxicity studies were performed 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

Core
Macrogol (containing butylhydroxytoluene)
Magnesium stearate

Film-coat
Hypromellose
Macrogol
Yellow iron oxide (E172)

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years

6.4 Special precautions for storage

There are no special storage instructions

6.5 Nature and contents of container

Aluminium foil blister packs containing 30 tablets.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Astellas Pharma Ltd
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Staines
TW18 3AZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00166/ 0199

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11th July 2005

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10th October 2006