Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tamsulosin 400 micrograms Modified-release Capsules, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 micrograms of tamsulosin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard

Orange body/olive-green cap. The capsules contain white to off-white spheres.

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 a day to be taken after breakfast or the first meal of the day.

Patients with renal impairment
No dose adjustment is warranted in renal impairment.

Patients with hepatic impairment
No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see also section 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 must be swallowed whole and must not be crunched or chewed as this interferes with the modified 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.
- 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 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 renal impaired patients (creatinine clearance of < 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, the 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 or glaucoma surgery in some patients on or previously treated with tamsulosin. IFIS may increase the risk of 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 or glaucoma 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 should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin should be used with caution in combination with strong and moderate inhibitors of CYP3A4 such as erythromycin (see 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 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, 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 chlormadinone.

Diclofenac and warfarin may increase the elimination rate of tamsulosin.

Tamsulosin has not been found to interact with amitriptyline, salbutamol, glibenclamide or finasteride during in vitro studies with liver microsomal fractions (representing the cytochrome P450-linked metabolising enzyme system).

Concomitant administration of tamsulosin with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and Cmax of tamsulosin by a factor of 2.8 and 2.2, respectively.

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

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

Concomitant administration of tamsulosin 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.

Concurrent administration with another α_1-adrenoreceptor antagonist can lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

Tamsulosin hydrochloride is not indicated for use in women.

Fertility

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 can occur.

4.8 Undesirable effects

	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <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					Blurred vision*, Impaired vision*
Cardiac disorders		Palpitations			
Vascular disorders		Orthostatic hypotension			
Respiratory, thoracic and mediastinal disorders		Rhinitis			Epistaxis*
Gastro-intestinal 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 including Retrograde ejaculation, Ejaculation failure			Priapism	
General disorders and administration site conditions		Asthenia			

*Observed in the post-marketing period

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
HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

4.9 Overdose

Symptoms

Overdosage with tamsulosin can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing. The largest dose of tamsulosin that was administered to an individual patient accidentally was 12 mg. The patient developed a headache, but did not require hospital treatment.

Management

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.

If large quantities of the medicinal product are involved, gastric lavage may be performed and activated charcoal and an osmotic laxative, such as sodium sulphate, may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in benign prostatic hypertrophy, alpha adrenoreceptor antagonists. ATC code: G04CA02

Mechanism of action

Tamsulosin binds selectively and competitively to postsynaptic α_1 adrenoreceptors, in particular to subtypes α_{1A} and $\alpha_{1D,}$ which convey smooth muscle contraction, thereby relaxing the 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, randomised, 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 randomised 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 stabilisation 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 rapidly absorbed from the intestines 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 the same daily meal.

Tamsulosin shows linear kinetics.

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 C_{max} 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.

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

Distribution

In humans, tamsulosin is more than 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. 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 sections 4.4 and 4.5).

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

Elimination

Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of the dose being present in unchanged form.

The elimination half-life of tamsulosin in patients is approximately 10 hours (when taken after a meal) and 13 hours in the steady state.

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

Content of capsule
Cellulose microcrystalline
Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate
Talc

Capsule shell
Gelatin
Indigo carmine (E 132)
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister packs: Store in the original package.
Capsule containers: Keep the container tightly closed.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blister packs in cardboard boxes containing 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 200 and multipacks containing 200 (2 packs of 100) modified-release capsules.

HDPE capsule containers with PP child-resistant closures containing 10, 14, 20, 28, 30, 50, 56, 60, 90, 100 or 200 modified-release capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd. T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/073/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2006
Date of last renewal: 23 March 2010

10 DATE OF REVISION OF THE TEXT

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