AUSTRALIAN PRODUCT INFORMATION
FLOSIX ® (TAMSULOSIN HYDROCHLORIDE) MODIFIED RELEASE TABLETS

1 NAME OF THE MEDICINE

Tamsulosin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Flosix 400 µg modified release tablet contains 400 µg tamsulosin hydrochloride.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Flosix 400 µg are brown, round, biconvex film-coated tablets with debossing '0.4' on one side and 'SZ' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

One tablet daily.

Method of administration

The tablet must be swallowed whole and not be broken, crunched or chewed, as this compromises the prolonged release properties of the tablet for the active ingredient.

Flosix can be taken on an empty stomach, or before, with or after food.

4.3 CONTRAINDICATIONS

- Hypersensitivity, including drug-induced angioedema to tamsulosin hydrochloride or any other component of the product.
- A history of orthostatic hypotension.
- **Severe** hepatic impairment (Child-Pugh scores > 9).
- **Severe** renal impairment with creatinine clearance of less than 10 mL/min.
- Concurrent use of another α_1-adrenoceptor inhibitor.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Syncope and Postural hypotension

Patients beginning treatment with Flosix tablets should be cautioned to avoid situations where injury could result should syncope occur. Postural hypotension can occur during treatment with Flosix, but rarely results in syncope. However, the patient should be warned of this possibility and advised to sit or lie down if symptoms of hypotension should occur.

Exclusion of prostatic carcinoma and other urological conditions

Carcinoma of the prostate and other conditions, which can cause the same symptoms as benign prostatic hyperplasia should be excluded before starting therapy with Flosix. Digital rectal examination and, as considered appropriate, determination of prostate specific antigen should be performed before treatment and at regular intervals afterwards.

Myocardial ischaemia

Patients with myocardial infarction or angina pectoris within the preceding six months were excluded from the Phase III clinical studies. As a result, the safety of Flosix in these patients has not been formally assessed.

Dizziness

As Flosix may cause dizziness, patients should be warned to take care whilst operating machinery or driving.

Intra-operative Floppy Iris Syndrome

Intra-operative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients taking or who have previously been treated with α_1-adrenoceptor antagonists, including tamsulosin. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin 1-2 weeks prior to cataract 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 cataract surgery.

The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract surgery is scheduled is not recommended. 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. This variant of small pupil syndrome is characterised by the combination of a flaccid iris that billows in response to intra-operative irrigation currents, progressive intra-operative miosis despite pre-operative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phaco-emulsification incisions.

During pre-operative assessment, ophthalmologists and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being, or have been, treated with α_1-adrenoceptor antagonists in order to ensure that appropriate measures will be in place to manage IFIS during surgery if it occurs. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilisation of iris hooks, iris dilator rings, or visco-elastic substances. The benefit of stopping α_1-adrenoceptor antagonist therapy prior to cataract or glaucoma surgery has not been established.

Sulfa Allergy

Cases of allergic reaction to tamsulosin in patients with a past history of sulphonamide allergy have been reported. If a patient reports a sulfa allergy, caution is warranted when administering Flosix.

Use in hepatic impairment

In a study of patients with moderate hepatic impairment, free tamsulosin levels remained unchanged after treatment with 400 µg tamsulosin hydrochloride in a modified release capsule

formulation when compared to normal subjects. Since the type of formulation will not affect the disposition of tamsulosin, no dose adjustment for tamsulosin tablets is expected in patients with mild to moderate hepatic impairment.

Severe hepatic impairment (Child-Pugh scores > 9) is a CONTRAINDICATION (Refer to Section 4.3 Contraindications).

Use in renal impairment

Severe renal impairment, with creatinine clearance of less than 10 mL/min is a CONTRAINDICATION, as these patients have not been studied (Refer to Section 4.3 Contraindications).

Use in the elderly

Refer to Section 4.2 Dose and method of administration.

Paediatric use

Flosix is not indicated for use in children.

Other populations

Flosix is not indicated for use in women.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interaction studies have only been performed in adults.

Drugs known to interact with tamsulosin

Concomitant cimetidine leads to a rise in plasma levels of tamsulosin, while furosemide leads to a fall (about 12% following a single 20 mg intravenous dose). However, as levels remain within the normal range, dosage need not be adjusted.

Concurrent administration of tamsulosin with other α_1-adrenoceptor antagonists is contraindicated because of the potential for hypotensive effects (see Section 4.3 Contraindications).

Drugs, which may interact with tamsulosin

Tamsulosin binds extensively to plasma proteins and may displace other protein-bound drugs. Clinical trial data are not available.

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

Drugs, which do not interact significantly with tamsulosin

Tamsulosin did not affect the pharmacokinetics of a single intravenous dose of digoxin 0.5 mg.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline.

General

Tamsulosin is metabolised in the liver, and may be expected to interact with other hepatically metabolised drugs. Pharmacokinetic studies in healthy volunteers revealed that concomitant administration with strong inhibitors of CYP3A4 or CYP2D6 may lead to increased exposure to tamsulosin. Concomitant administration with ketoconazole (a known CYP3A4 inhibitor) resulted in an increased C_{max} and AUC of tamsulosin. Tamsulosin 400 µg should not be used in combination with strong inhibitors of CYP3A4 in patients known to be CYP2D6 poor metabolizers. Concomitant administration with paroxetine (a known CYP2D6 inhibitor) results in an increased C_{max} and AUC of tamsulosin. Tamsulosin should therefore be used with caution in patients who are taking other drugs, particularly those which undergo hepatic metabolism.

Other in vitro findings

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.

An *in vitro* study using human liver microsomal fractions showed no effect of amitriptyline, salbutamol, glibenclamide and finasteride on the rate of disappearance of tamsulosin. The clinical relevance of these findings is uncertain.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reproduction toxicity in rats has been conducted.

α-adrenoceptor antagonists are known to reduce male fertility by affecting penile erection, emission and/or ejaculation. In male rats, a severe reduction in male copulation rate and fertility was observed after a single dose or after repeated oral doses of tamsulosin. Spermatogenesis was not affected in the rat studies, and the effect on fertility was reversible. The no effect dose on male rat fertility was associated with plasma tamsulosin levels (AUC) at least 50% of those expected in human males treated with tamsulosin tablets.

Treatment of female rats with tamsulosin caused disruption of the oestrus cycle and a severe reduction in fertility, due to interference of fertilisation with the ova. These effects were shown to be reversible.

Use in pregnancy

Category B2

Flosix is intended for use only in males. Tamsulosin is not indicated for use in women.

Tamsulosin, at oral doses causing maternal toxicity, was not embryotoxic or teratogenic when administered during gestation in rats (doses up to 300 mg/kg/day) or rabbits (doses up to 50 mg/kg/day). However, administration of tamsulosin during the peri-/post-natal period was associated with a higher incidence of stillbirths and reduced pup weight gain after birth. No adverse effects on development or reproductive performance were observed on surviving pups; however, there is some evidence for impairment of offspring reproductive capacity when maternal treatment with tamsulosin is started before pregnancy.

Use in lactation

Flosix is intended for use only in males.

In female rats, tamsulosin and/or its metabolites were shown to pass into milk after oral administration of the drug during lactation. The effect on the newborn is not known.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As tamsulosin may cause dizziness, patients should be warned to take care whilst operating machinery or driving.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Priapism

Rarely, tamsulosin, like other α_1 antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction.

Abnormal ejaculation

Patients should be advised on the potential for abnormal ejaculation to occur upon commencement of tamsulosin treatment. Retrograde ejaculation and ejaculation failure are the most commonly reported abnormal ejaculation events associated with the use of tamsulosin (see Table 1).

Clinical Trials

Table 1 shows the incidence of undesirable effects following 400 μg tamsulosin treatment. This data is based on a phase 3 clinical study in which there were no relevant differences between the treatment and placebo groups in the percentage of patients reporting at least 1 Treatment Emergent Adverse Event (TEAE). Most TEAEs were of mild or moderate intensity. The most frequent TEAEs were ejaculation disorders. These are TEAEs that are often associated with α_1-AR antagonists.

Table 1: Adverse events associated with tamsulosin in a placebo-controlled study.

	Placebo N = 356	**Tamsulosin N = 360**
Non-cardiovascular class effects		
Retrograde ejaculation	1 (0.3%)	6 (1.7%)
Ejaculation failure	0 (0.0%)	0 (0.0%)
Semen volume reduced	0 (0.0%)	1 (0.3%)
Ejaculation delayed	0 (0.0%)	1 (0.3%)
Ejaculation disorder NOS	0 (0.0%)	0 (0.0%)
Abnormal ejaculation pooled	1 (0.3%)	7 (1.9%)
Headache NOS	4 (1.1%)	3 (0.8%)
Asthenia	1 (0.3%)	1 (0.3%)
Fatigue	1 (0.3%)	3 (0.8%)
Somnolence	0 (0.0%)	0 (0.0%)
Rhinitis NOS	0 (0.0%)	1 (0.3%)
Nasal congestion	0 (0.0%)	1 (0.3%)
Nasal obstruction	0 (0.0%)	0 (0.0%)
SUB-TOTAL	7 (2.0%)	16 (4.4%)
Cardiovascular class effects		
Dizziness	5 (1.4%)	5 (1.4%)
Dizziness aggravated	0 (0.0%)	0 (0.0%)
Dizzy spell	0 (0.0%)	0 (0.0%)

	Placebo N = 356	Tamsulosin N = 360
Dizziness pooled	5 (1.4%)	5 (1.4%)
Palpitations	2 (0.6%)	2 (0.6%)
Tachycardia NOS	0 (0.0%)	1 (0.3%)
Hypotension NOS	1 (0.3%)	0 (0.0%)
Orthostatic hypotension	0 (0.0%)	0 (0.0%)
Dizziness postural	0 (0.0%)	0 (0.0%)
Syncope	0 (0.0%)	0 (0.0%)
Orthostatic/circulatory collapse	0 (0.0%)	0 (0.0%)
Depressed level of/loss of consciousness	0 (0.0%)	1 (.03%)
SUB-TOTAL	8 (2.2%)	9 (2.5%)
TOTAL	13 (3.7%)	25 (6.9%)

NOS = Not Otherwise Specified.

A patient may experience a TEAE more than once or may experience more than one TEAE within the same System Organ Class. Data from clinical trial study 617-CL-307

The following treatment-related adverse events were reported from clinical trials, where Common is ≥ 1% and < 10%; Uncommon is ≥ 0.1% and < 1%; Rare is ≥ 0.01% and < 0.1%; and Very rare is < 0.01%.

Cardiac disorders
Uncommon: palpitations

Gastro-intestinal disorders
Uncommon: constipation, diarrhoea, nausea, vomiting
Not known: dry mouth

General disorders
Uncommon: asthenia

Nervous system disorders
Common: dizziness (1.3%), insomnia
Uncommon: headache
Rare: syncope

Reproductive system disorders
Common: ejaculation disorders
Very rare: priapism

Respiratory, thoracic and mediastinal disorders
Uncommon: rhinitis

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, urticaria
Rare: angioedema
Very rare: Stevens-Johnson syndrome

Vascular disorders
Uncommon: postural hypotension.

Post-marketing experience

The following events have been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency.

General disorders: chest discomfort that could be caused or associated with other medical conditions such as respiratory conditions or cardiac disease.

Vision disorders: blurred vision, vision impairment.

During cataract and glaucoma surgery, a variant of small pupil syndrome known as Intra-operative Floppy Iris Syndrome (IFIS) has been reported during post-marketing surveillance in association with α_1-adrenoceptor antagonist therapy (See Section 4.4 Special warnings and precautions for use – Intra-operative Floppy Iris Syndrome).

Skin and subcutaneous tissue disorders: skin desquamation, dermatitis exfoliative, erythema multiforme, Stevens-Johnson syndrome, photosensitivity reaction.

Respiratory, thoracic and mediastinal disorder: epistaxis

In addition to the adverse events listed above, atrial fibrillation, arrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mmHg), vomiting and diarrhoea were observed, which were treated with fluid replacement and the patient could be discharged the same day.

If acute hypotension occurs after overdosage, cardiovascular support should be given and maintained. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this is insufficient then volume expanders and, when necessary, vasopressors could be administered. 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.

Flosix is a modified release formulation. The signs and symptoms of overdose may be delayed or prolonged from the time of ingestion.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The tone of the human prostate smooth muscle is maintained primarily by noradrenaline released from adrenergic nerves and stimulating post-junctional α_1-adrenoceptors. This provides the rationale for the use of α_1-adrenoceptor antagonists for lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH).

Pharmacological studies have established that tamsulosin is a selective, potent and competitive α_1-adrenoceptor antagonist and that it has a greater affinity for the α_{1A}-receptor subtype, predominantly present in the human prostate.

α_1-adrenoceptor antagonists generally can reduce blood pressure by lowering peripheral resistance. However, no reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

The binding of tamsulosin to α_1-adrenoceptors in the prostate results in relaxation of prostate smooth muscle followed by improvements in urodynamics. Thus, tamsulosin increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra and thereby relieving obstruction.

It also improves the symptoms related to bladder instability and tension of the smooth muscle of the lower urinary tract.

These effects on urinary storage and voiding symptoms are maintained during long-term therapy. The need for surgery or catheterisation is significantly delayed.

Clinical trials

The efficacy of tamsulosin tablets has been evaluated in 2 randomised, placebo-controlled studies: the phase 2 dose-response study 617-CL-303 and the phase 3 study 617-CL-307. A total of 2962 patients were studied, of which 560 were treated with 0.4 mg of tamsulosin tablets and 564 were treated with placebo. The remaining subjects were treated with 0.4 mg (capsules), 0.8 mg and 1.2 mg (tablets) doses of tamsulosin hydrochloride.

Inclusion Criteria

In both studies the inclusion criteria were: male patients aged ≥ 45 years, diagnosed as having lower urinary tract symptoms (LUTS) suggestive of BPH, with voiding/obstructive symptoms (including incomplete emptying of the bladder, intermittency, poor stream or hesitancy), and/or storage/irritative/filling symptoms (including daytime frequency, urgency or nocturia).

These patients had a total International Prostate Symptom Score (I-PSS) of ≥ 13, both at enrolment (Visit 1) and at baseline after the 2-week placebo run-in period (Visit 2). At enrolment, they also had to have a maximum flow rate (Q_{max}) of ≥ 4.0 mL/s and ≤ 12.0 mL/s, with a voided volume ≥ 120 mL during free flow.

Patients with cardiac ischaemia were excluded from participation in these trials. Safety in such patients has not been formally assessed.

Study 617-CL-303:

Study 617-CL-303 was a multi-center, double-blind, randomised, placebo-controlled, parallel group, dose–response study. In this study, 211 patients received placebo and 203 patients

received 400 μg of tamsulosin tablets once daily for 12 weeks of the double-blind randomised treatment. The results of study 617-CL-303 are summarised in Table 2.

Study 617-CL-307:

Study 617-CL-307 was a multi-center, double-blind, randomised, placebo and active-controlled, parallel group study. In this study, 353 patients received placebo and 357 patients received 400 μg of tamsulosin tablets once daily for 12 weeks of the double-blind randomised treatment. The results of study 617-CL-307 are summarised in Table 3.

The primary efficacy parameter in both studies following 400 μg tamsulosin tablets treatment was the change from baseline to endpoint in total I-PSS scores. The secondary efficacy analyses contained the changes from baseline in voiding and storage I-PSS sub-scores, and I-PSS Quality of Life scores.

The I-PSS questionnaire was developed and validated by the American Urological Association (I-PSS previously called the AUA Symptom Index) and consisted of 7 questions evaluating the frequency of 7 urinary symptoms. These included 4 voiding symptoms (poor stream, hesitancy, intermittency and incomplete bladder emptying) and 3 storage symptoms (daytime frequency, nocturia and urgency). The patient rated each of the 7 symptoms on a scale of 0-5 of increasing symptom severity. The total score could therefore range from 0-35, the voiding sub-score from 0-20 and the storage sub-score from 0-15. The questionnaire was adopted by the World Health Organization, who added a further question assessing the impact of the urinary symptoms on the Quality of Life. The Quality of Life question asked how the patient would feel about his current level of symptoms for the rest of his life, ranging from 1 (delighted) to 6 (terrible).

Table 2: Results from clinical trial 617-CL-303 showing mean (SD) changes from baseline scores following daily treatment with placebo or 400 μg of tamsulosin tablets.

Parameter	Treatment	Baseline mean (SD)	Endpoint mean (SD)	Mean change (SD)	Mean % change (SD)	Mean difference vs placebo (95% CI)	P value vs placebo
Total I-PSS	Placebo Tamsulosin	17.8 (4.0) 18.0 (4.3)	11.7 (6.1) 10.4 (5.5)	-6.0 (5.4) -7.6 (5.3)	-34.5 (30.1) -42.4 (27.6)	-1.6 (-2.5,-0.6)	0.0016*
Voiding I-PSS	Placebo Tamsulosin	10.4 (3.2) 10.6 (3.3)	6.9 (4.1) 5.7 (3.6)	-3.6 (3.5) -4.8 (3.8)	-35.1 (33.6) -44.2 (32.9)	-1.2 (-1.9,-0.6)	
Storage I-PSS	Placebo Tamsulosin	7.3 (2.6) 7.4 (2.7)	4.9 (2.7) 4.6 (2.7)	-2.4 (2.9) -2.8 (2.5)	-30.0 (40.0) -37.2 (31.9)	-0.3 (-0.8, 0.2)	
Quality of Life **	Placebo Tamsulosin	3.7 (1.0) 3.7 (1.0)	2.8 (1.2) 2.4 (1.3)	-0.9 (1.3) -1.3 (1.3)	–	-0.4 (-0.6,-0.2)	

Table 3: Results from clinical trial 617-CL-307 showing mean (SD) changes from baseline scores following daily treatment with placebo or 400 μg of tamsulosin tablets.

Parameter	Treatment	Baseline mean (SD)	Endpoint mean (SD)	Mean change (SD)	Mean % change (SD)	Mean difference vs placebo (95% CI)	P value vs placebo
Total I-PSS	Placebo Tamsulosin	18.3 (4.5) 18.5 (4.4)	12.4 (6.4) 10.8 (6.2)	-5.8 (5.6) -7.7 (5.8)	-32.0 (30.8) -41.7 (29.6)	-1.7 (-2.5,-1.0)	< 0.0001*
Voiding I-PSS	Placebo Tamsulosin	10.6 (3.4) 10.7 (3.4)	7.0 (4.1) 6.0 (4.2)	-3.7 (3.8) -4.7 (4.0)	-32.6 (41.4) -43.9 (34.4)	-1.0 (-1.5,-0.5)	

Parameter	Treatment	Baseline mean (SD)	Endpoint mean (SD)	Mean change (SD)	Mean % change (SD)	Mean difference vs placebo (95% CI)	P value vs placebo
Storage I-PSS	Placebo Tamsulosin	7.6 (2.6) 7.8 (2.6)	5.4 (3.0) 4.8 (2.8)	-2.2 (2.7) -3.0 (2.8)	-27.2 (34.6) -37.4 (32.5)	-0.7 (-1.1,-0.4)	
Quality of Life **	Placebo Tamsulosin	3.8 (1.0) 3.8 (1.0)	2.7 (1.3) 2.4 (1.3)	-1.1 (1.3) -1.4 (1.3)	–	1.53 (1.18,2.00)	

* = statistically significant
I-PSS = International Prostate Symptom Score.
SD = Standard Deviation and
CI = Confidence Interval
** = Odds ratio

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Flosix is a modified (prolonged) release tablet. The formulation provides consistent slow release of tamsulosin, which is maintained over the whole pH range encountered in the gastro-intestinal tract, resulting in an adequate exposure, with little fluctuation, over 24 hours.

Tamsulosin administered as tamsulosin tablets is absorbed from the intestine. Of the administered dose, approximately 55 to 59% is estimated to be absorbed. The rate and extent of absorption of tamsulosin hydrochloride administered as tamsulosin tablets are only slightly affected by food, but this is unlikely to be clinically significant.

Tamsulosin hydrochloride administered as tamsulosin tablets exhibits near linear pharmacokinetics (plasma concentrations C_{max} and AUC vs dose) over the dosage range 0.4 mg through 0.8 mg to 1.2 mg once daily. Steady state is reached by day 4 of multiple dosing. The pharmacokinetics of a 400 µg once daily dose of tamsulosin hydrochloride as tamsulosin tablets as a single dose under fasted conditions, and steady state under fed and fasted conditions are shown in Table 4.

Table 4: Mean (SD) pharmacokinetic parameters following once daily dosing with 400 µg of tamsulosin hydrochloride as tamsulosin tablets.

Parameter	400 µg single dose to fasted healthy males (n = 12)	400 µg multiple dose to healthy males at steady state (n = 24)	
		Fasted	Fed
T_{max} (hr)	8.51 (7.32)	4.75 (1.65)	4.16 (1.47)
C_{max} (ng/mL)	5.88 (2.61)	10.7 (5.5)	11.1 (3.7)
C_{24} (ng/mL)	4.16 (1.98)	4.6 (3.6)	4.8 (2.7)
AUC* (ng.hr/mL)	201.6 (104.0)	162.4 (104.2)	165.9 (69.1)
$T_{½}$ (hr)	18.67 (6.99)	15.6 (4.4)	14.6 (7.0)
TPF	NA	0.404 (0.144)	0.421 (0.116)

* AUC_{0-inf} for single dose; AUC_{0-24} for multiple dose
TPF: trough-peak fluctuation. NA: not applicable.

As a result of the prolonged release characteristic of tamsulosin, the trough concentrations – at steady state, of tamsulosin hydrochloride in plasma amount to approximately 40% of the peak plasma concentrations, under fasted and fed conditions.

There is a considerable inter-patient variation in the plasma concentrations of tamsulosin hydrochloride, after both single and multiple dosing.

Following oral administration of a single dose of tamsulosin 400 µg to healthy adult males under fasted and fed conditions, a mean peak plasma concentration (C_{max}) of tamsulosin of approximately 4.72 ng/mL and 8.30 ng/mL respectively was achieved within approximately 4.75 hours and 5.63 hours respectively (T_{max}).

Following oral administration of a multiple dose of tamsulosin 400 µg to healthy adult males at steady state under fasting conditions, a mean peak plasma concentration (C_{max}) of tamsulosin of approximately 8.77 ng/mL was achieved within approximately 4.22 hours (T_{max}).

Distribution

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

Metabolism

Tamsulosin 400 µg contains tamsulosin as the R(-) isomer. In humans, there is no *in vivo* conversion to the less active S(+) isomer. Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged drug. Tamsulosin is metabolised in the liver. *In vitro* results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin metabolism by other CYP isozymes. Inhibition of hepatic drug metabolizing enzymes may lead to increased exposure to tamsulosin (see Section 4.5 Interactions with other medicines and other forms of interactions – General). In rats, tamsulosin was seen to cause minimal induction of microsomal liver enzymes. No dose adjustment is warranted in hepatic insufficiency. (See Section 4.3 Contraindications).

None of the metabolites is more active than the original precursor compound.

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 tablets.

No dose adjustment is warranted in renal impairment (see Section 4.3 Contraindications).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vivo and *in vitro* genotoxicity has been conducted.

Tamsulosin hydrochloride produced no evidence of genotoxic potential in assays for gene mutation (Ames reverse mutation test and mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells and mouse micronucleus assay) and other genotoxic effects (unscheduled DNA repair synthesis and *in vivo* sister chromatid exchange).

Carcinogenicity

Carcinogenicity studies in mice and reproduction toxicity studies in rats have been conducted.

Oral (dietary) administration of tamsulosin for up to 2 years in rats and mice was associated with an increased incidence of pituitary adenoma, mammary gland hyperplasia, mammary gland fibroadenoma and (in mice only) mammary gland adenocarcinoma. These effects occurred at plasma tamsulosin concentrations (AUC) up to 10 times lower than those expected in men undergoing treatment with tamsulosin tablets, but they were observed only in female animals and are probably due to the hyperprolactinaemic effect of tamsulosin. It is not known if tamsulosin elevates prolactin during prolonged administration in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in female rodents is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following inactive (excipients) ingredients:

Excipients core: microcrystalline cellulose, hyprolose, polyethylene oxide, butylated hydroxytoluene, magnesium stearate, colloidal anhydrous silica.

Excipients coating: hypromellose, hyprolose, macrogol 400, titanium dioxide, purified talc, quinoline yellow, cochineal, iron oxide black.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

For information on interactions with other medicines and other forms of interactions, refer to Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

Flosix 400 µg are packaged in Alu/Alu blister packs of 10 or 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Tamsulosin hydrochloride is slightly soluble in water, freely soluble in formic acid, and slightly soluble in anhydrous ethanol. It is stable in an acid environment.

The pH of tamsulosin is 4.8-5.3 with a pK_a of 8.4 (secondary amine) and 10.7 (sulphonamide) and a partition coefficient of 2.2.

Chemical structure

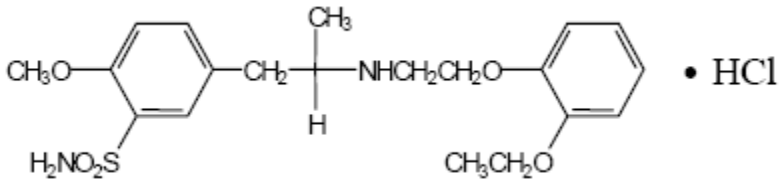

Figure 1. Chemical structure of Tamsulosin hydrochloride

Chemical formula: 5-[(2*R*)-2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride

Molecular formula: $C_{20}H_{28}N_2O_5S.HCl$

Molecular weight: 445.0

CAS number

106463-17-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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Telephone No: 1800 726 369

9 DATE OF FIRST APPROVAL

20/07/2020

10 DATE OF REVISION

09/10/2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Chest discomfort added as a post-marketing adverse effect