AUSTRALIAN PRODUCT INFORMATION
FLOMAXTRA® (TAMSULOSIN HYDROCHLORIDE) PROLONGED RELEASE TABLETS

1 NAME OF THE MEDICINE

Tamsulosin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FLOMAXTRA® is a film-coated, prolonged release tablet containing 400 µg tamsulosin hydrochloride, an α1-adrenoceptor blocking agent, equivalent to 367 µg of tamsulosin per tablet

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

3 PHARMACEUTICAL FORM

FLOMAXTRA® is a film-coated, prolonged release tablet.

FLOMAXTRA® tablets are yellow, approximately 9 mm, round, bi-convex, film-coated and debossed with the code '04' on one 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

One tablet daily.

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.

FLOMAXTRA® 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 10mL/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 FLOMAXTRA® tablets should be cautioned to avoid situations where injury could result should syncope occur. Postural hypotension can occur during treatment with FLOMAXTRA®, 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 FLOMAXTRA®. 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 FLOMAXTRA® in these patients has not been formally assessed.

Dizziness

As FLOMAXTRA® 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) has been observed during cataract and glaucoma surgery in some patients taking or who have previously been treated with α1-adrenoceptor antagonists, including tamsulosin. 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 α1-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 α1-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 FLOMAXTRA®.

Use in hepatic impairment

In a study of patients with moderate hepatic impairment, free tamsulosin levels remained unchanged after treatment with Flomax® (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 FLOMAXTRA® 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 10mL/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

FLOMAXTRA® is not indicated for use in children.

Other populations

FLOMAXTRA® 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

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 FLOMAXTRA® with other α1-adrenoceptor antagonists is contraindicated because of the potential for hypotensive effects (Refer to 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
FLOMAXTRA® 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 Cmax 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) resulted in an increased Cmax 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

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 FLOMAXTRA®.

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 – Pregnancy Category B2

FLOMAXTRA® is intended for use only in males.

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.

FLOMAXTRA® 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 FLOMAXTRA® 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 alpha-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 FLOMAXTRA® treatment. Retrograde ejaculation is the most commonly reported abnormal ejaculation event associated with the use of FLOMAXTRA® (see Table 1).

Clinical trials

Table 1 shows the incidence of undesirable effects following 400 µg FLOMAXTRA® 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 α1-AR antagonists.

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

	Placebo N=356	FLOMAXTRA 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%)
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 (0.3%)
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.

General disorders

Uncommon: asthenia.

Nervous system disorders

Common: dizziness (1.3%), insomnia.
Uncommon: headache.
Rare: syncope.

Reproductive system disorders

Common: ejaculation disorder
Very rare: priapism.

Respiratory, thoracic and mediastinal disorders

Uncommon: rhinitis.

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, urticaria.
Rare: angioedema.

Vascular disorders

Uncommon: postural hypotension.

Post-marketing experience

The following events have also 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.

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 in association with α1-adrenoceptor antagonist therapy (Refer to 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.

Respiratory, thoracic and mediastinal disorders: epistaxis.

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 mm Hg), 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.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (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 α1-adrenoceptors. This provides the rationale for the use of α1-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.

α1-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 FLOMAXTRA®.

The binding of tamsulosin to α_1-adrenoceptors in the prostate results in relaxation of prostate smooth muscle followed by improvements in urodynamics. Thus, FLOMAXTRA® 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 FLOMAXTRA® 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 FLOMAXTRA® 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 (Qmax) 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 FLOMAXTRA® 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 FLOMAXTRA® 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 FLOMAXTRA® 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 FLOMAXTRA®.

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 FLOMAXTRA®	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 FLOMAXTRA®	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 FLOMAXTRA®	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 FLOMAXTRA®	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 FLOMAXTRA®.

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 FLOMAXTRA®	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 FLOMAXTRA®	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)	
Storage I-PSS	Placebo FLOMAXTRA®	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 FLOMAXTRA®	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

FLOMAXTRA® is a prolonged release tablet of the non-ionic gel matrix type. The FLOMAXTRA® 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 FLOMAXTRA® 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 FLOMAXTRA® tablets are only slightly affected by food, but this is unlikely to be clinically significant.

Tamsulosin hydrochloride administered as FLOMAXTRA® tablets exhibits near linear pharmacokinetics (plasma concentrations Cmax 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 FLOMAXTRA® 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 FLOMAXTRA® 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 FLOMAXTRA®, 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.

Distribution

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

Metabolism

FLOMAXTRA® 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 metabolising enzymes may lead to increased exposure to tamsulosin (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). In rats, tamsulosin was seen to cause minimal induction of microsomal liver enzymes. No dose adjustment is warranted in hepatic insufficiency (Refer to 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 FLOMAXTRA®.

No dose adjustment is warranted in renal impairment (Refer to Section 4.3 – CONTRAINDICATIONS).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vivo and in vitro genotoxicity studies have been conducted.

Tamsulosin HCl 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

Reproduction toxicity studies in rats and carcinogenicity studies in mice and 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 FLOMAXTRA®, but they were observed only in female animals and are probably due to the hyperprolactinaemic effect of tamsulosin. It is not known if FLOMAXTRA® 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

FLOMAXTRA® also contains macrogol 7,000,000, macrogol 8,000, magnesium stearate, butylated hydroxytoluene, colloidal silica anhydrous, hypromellose, iron oxide yellow. None of the excipients is derived from animal sources.

6.2 INCOMPATIBILITIES

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

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

FLOMAXTRA® should be stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

FLOMAXTRA® is available in packs of 10 or 30 tablets supplied in aluminium foil blister strips, each of which contains 10 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

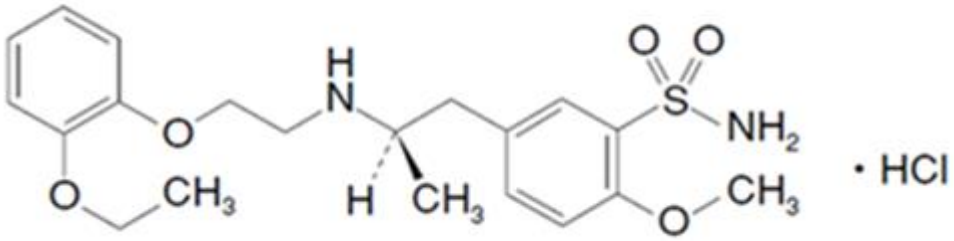
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Tamsulosin hydrochloride is sparingly soluble in water (1:85) and slightly soluble in alcohol. It is stable in an acid environment.

Chemical structure

The chemical structure of tamsulosin hydrochloride is:



The chemical name is (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. The molecular weight is 444.98.

CAS number

CAS-106463-17-6 (hydrochloride)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Astellas Pharma Australia Pty Ltd
6 Eden Park Drive
Macquarie Park NSW 2113

Tel: 1800 751 755 (Medical Information)
Email: aaumedinfo@astellas.com (Medical Information)
Website: www.astellas.com/au

9 DATE OF FIRST APPROVAL

18 January 2006

10 DATE OF REVISION

9 January 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Drug-induced angioedema added to section
4.8	Stevens-Johnson syndrome added as a post-marketing adverse effect