URISOLIN
(Tamsulosin HCl)

0.4 mg

Capsule

COMPOSITION

Each capsule contains:
Tamsulosin hydrochloride U.S.P. 0.4mg
(as modified release pellets)

THERAPEUTIC INDICATIONS

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

DOSAGE AND ADMINISTRATION

One capsule daily after breakfast or after the first daily meal.

Hepatic/renal impairment
No dose adjustment is warranted in renal impairment.
No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency

Pediatric population
The safety and efficacy of tamsulosin hydrochloride in children < 18 years have not been established.

Method of Administration

Oral use.
The capsule is swallowed whole, without crushing or chewing, because otherwise the controlled release of the active ingredient would be affected.

CONTRAINDICATIONS

- Hypersensitivity to the active substance.

- History of orthostatic hypotension.

- Severe hepatic insufficiency.

- Micturition syncope history.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other α_1-adrenoceptors antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin hydrochloride 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 hydrochloride 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 patients with severe renal impairment (creatinine clearance of < 10 ml/min) should be approached with caution, as these patients have not been studied.

Angioedema has been rarely reported after the use of tamsulosin. In case of angioedema, 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 surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation.

Discontinuing tamsulosin hydrochloride 1 – 2 weeks prior to cataract 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 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.

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

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

DRUG INTERACTIONS

Interaction studies have only been performed in adults.

No interactions have been seen when tamsulosin hydrochloride 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 chlormadinon.

Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

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 C_{max} 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 in patients with poor metaboliser CYP2D6 phenotype.

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

Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a C_{max} 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 of other α_1-adrenoceptor antagonists could lead to hypotensive effects.

EFFECTS ON ABILITY TO DRIVE

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.

FERTILITY, PREGNANCY AND LACTATION

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 authorization phase.

ADVERSE DRUG REACTIONS

Tabulated list of adverse reactions

The frequency of adverse reactions of tamsulosin listed below is defined using the following convention: 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).

MedDRA system organ class	**Frequency**	**Adverse reaction**

Nervous system disorders	Common	Dizziness (1.3%)
	Uncommon	Headache
	Rare	Syncope
Eye disorders	Not known	Vision blurred*, visual impairment*
Cardiac disorders	Uncommon	Palpitations
Vascular disorders	Uncommon	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis
	Not known	Epistaxis*
Gastrointestinal disorders	Uncommon	Constipation, diarrhoea, nausea, vomiting
	Not known	Dry mouth*
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus, urticaria
	Rare	Angioedema
	Very rare	Stevens-Johnson syndrome
	Not known	Erythema multiforme*, dermatitis exfoliative*
Reproductive system and breast disorders	Common	Ejaculation disorder, retrograde ejaculation, ejaculation failure
	Very rare	Priapism
General disorders and administration site conditions	Uncommon	Asthenia

* Observed post-marketing.

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.

Post-marketing experience:

In addition to the adverse events listed above, atrial fibrillation, arrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin hydrochloride 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 authorization 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 pv@searlecompany.com

OVERDOSE

Symptoms

Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

Treatment

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. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic category: Adrenergic α_1-receptors antagonist.

ATC: G04CA02.

The product is designed exclusively for the treatment of diseases of the prostate.

Mechanism of action

Tamsulosin binds selectively and competitively to post-synaptic α_1-adrenoreceptors, prevailingly their subtypes designated α_{1A} and α_{1D}. Thus relaxation of smooth muscles of the prostate and urethra is achieved, which leads to a reduction of tonus and an improvement of the urinary flow.

Pharmacodynamic effects

Tamsulosin increases the maximum urinary flow. Due to relaxation of smooth muscles in the prostate and the urethra, obstruction is decreased, which leads to alleviation of voiding symptoms.

Tamsulosin also alleviates the storage symptoms in the development of which also the instability of the urinary bladder is involved at a significant extent. The effects on symptoms of filling and depletion of the urinary bladder persist during long-term treatment. The necessity of surgical treatment or catheterization is significantly delayed owing to these effects.

α_1-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.

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.

Pharmacokinetic properties

Absorption

Tamsulosin is absorbed from the intestinal tract and its bioavailability is almost complete. The absorption of tamsulosin decreases if the product is administered shortly after the meal. The uniformity of absorption may be supported via using the product tamsulosin capsules always after the same daily meal.

Kinetics of tamsulosin is linear.

After a single dose of tamsulosin taken after a full meal, the peak plasma levels are achieved at approximately 6 hours. 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, approximately 99% of tamsulosin is bound to plasma proteins and its distribution volume is small (approximately 0.2 l/kg).

Biotransformation

Tamsulosin has a low first pass metabolic effect. The majority of tamsulosin is present in plasma in an unchanged form. Tamsulosin is metabolized in the liver.

In studies on rats, an induction of microsomal liver enzymes induced by tamsulosin has not been practically observed.

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.

Dosage adjustment is not necessary in mild hepatic insufficiency.

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; approximately 9% of the dose given is released in an 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.

In case of renal affections, no reduction of tamsulosin doses is substantiated.

Summary of Clinical Studies

Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received TAMSULOSIN capsules 0.4 mg once daily, 491 received TAMSULOSIN capsules 0.8 mg once daily, and 802 were control patients) in the U.S. and Europe.

In the two U.S. placebo-controlled, double-blind, 13-week, multicenter studies [Study 1 (US92-03A) and Study 2 (US93-01)], 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, TAMSULOSIN capsules 0.4 mg once daily, or TAMSULOSIN capsules 0.8 mg once daily. Patients in TAMSULOSIN capsules 0.8 mg once-daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8 mg once-daily dose. The primary efficacy assessments included: 1) total American Urological Association (AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and 2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decreased urinary obstruction.

Mean changes from baseline to Week 13 in total AUA Symptom Score were significantly greater for groups treated with TAMSULOSIN capsules 0.4 mg and 0.8 mg once daily compared to placebo in both U.S. studies (Table 3, Figures 2A and 2B). The changes from baseline to Week 13 in peak urine flow rate were also significantly greater for the TAMSULOSIN capsules 0.4 mg and 0.8 mg once-daily groups compared to placebo in Study 1, and for the TAMSULOSIN capsules 0.8 mg once-daily group in Study 2 (Table 3, Figures 3A and 3B). Overall there were no significant differences in improvement observed in total AUA Symptom Scores or peak urine flow rates between the 0.4 mg and the 0.8 mg dose groups with the exception that the 0.8 mg dose in Study 1 had a significantly greater improvement in total AUA Symptom Score compared to the 0.4 mg dose.

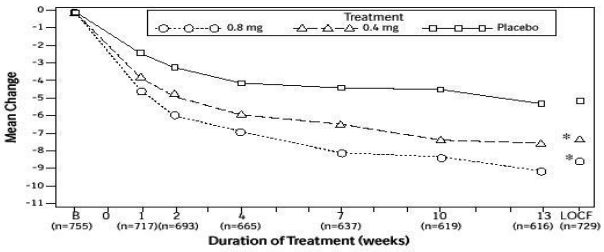
Table 3 Mean (±S.D.) Changes from Baseline to Week 13 in Total AUA Symptom Score and Peak Urine Flow Rate (mL/sec)**

	Total AUA Symptom Score		**Peak Urine Flow Rate**	
	Mean Baseline Value	**Mean Change**	**Mean Baseline Value**	**Mean Change**
* Statistically significant difference from placebo (p-value ≤0.050; Bonferroni-Holm multiple test procedure).				
** Total AUA Symptom Scores ranged from 0 to 35.				
† Peak urine flow rate measured 4 to 8 hours post dose at Week 13.				
‡ Peak urine flow rate measured 24 to 27 hours post dose at Week 13.				
Week 13: For patients not completing the 13-week study, the last observation was carried forward.				
Study 1†				
TAMSULOSIN capsules 0.8 mg once daily	19.9 ± 4.9 n=247	-9.6* ± 6.7 n=237	9.57 ± 2.51 n=247	1.78* ± 3.35 n=247
TAMSULOSIN capsules 0.4 mg once daily	19.8 ± 5.0 n=254	-8.3* ± 6.5 n=246	9.46 ± 2.49 n=254	1.75* ± 3.57 n=254
Placebo	19.6 ± 4.9 n=254	-5.5 ± 6.6 n=246	9.75 ± 2.54 n=254	0.52 ± 3.39 n=253
Study 2 ‡				
TAMSULOSIN capsules 0.8 mg once daily	18.2 ± 5.6 n=244	-5.8* ± 6.4 n=238	9.96 ± 3.16 n=244	1.79* ± 3.36 n=237
TAMSULOSIN capsules 0.4 mg once daily	17.9 ± 5.8 n=248	-5.1* ± 6.4 n=244	9.94 ± 3.14 n=248	1.52 ± 3.64 n=244
Placebo	19.2 ± 6.0 n=239	-3.6 ± 5.7 n=235	9.95 ± 3.12 n=239	0.93 ± 3.28 n=235

Mean total AUA Symptom Scores for both TAMSULOSIN capsules 0.4 mg and 0.8 mg once-daily groups showed a rapid decrease starting at 1 week after dosing and remained decreased through 13 weeks in both studies (Figures 2A and 2B).

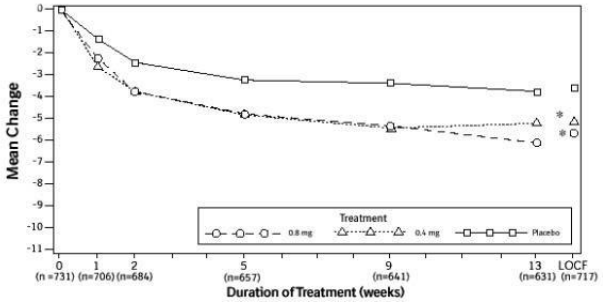
In Study 1, 400 patients (53% of the originally randomized group) elected to continue in their originally assigned treatment groups in a double-blind, placebo-controlled, 40-week extension trial (138 patients on 0.4 mg, 135 patients on 0.8 mg, and 127 patients on placebo). Three hundred twenty-three patients (43% of the originally randomized group) completed one year. Of these, 81% (97 patients) on 0.4 mg, 74% (75 patients) on 0.8 mg, and 56% (57 patients) on placebo had a response ≥25% above baseline in total AUA Symptom Score at one year.

Figure 2A Mean Change from Baseline in Total AUA Symptom Score (0-35) Study 1



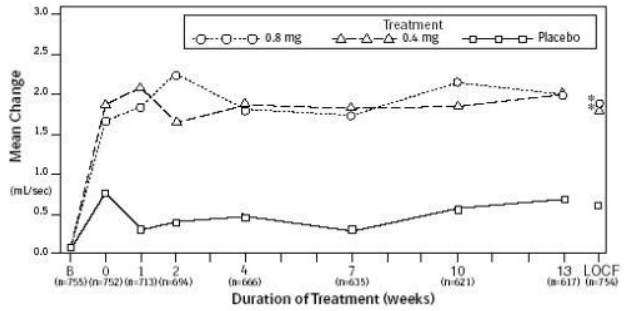
* indicates significant difference from placebo (p-value ≤0.050).
B = Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0.
Subsequent values are observed cases.
LOCF = Last observation carried forward for patients not completing the 13-week study.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Total AUA Symptom Scores range from 0 to 35.

Figure 2B Mean Change from Baseline in Total AUA Symptom Score (0-35) Study 2



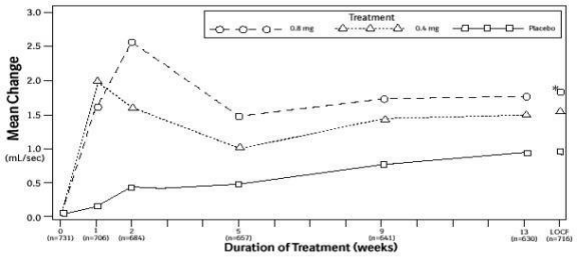
* indicates significant difference from placebo (p-value ≤0.050).
Baseline measurement was taken Week 0. Subsequent values are observed cases.
LOCF = Last observation carried forward for patients not completing the 13-week study.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Total AUA Symptom Scores range from 0 to 35.

Figure 3A Mean Increase in Peak Urine Flow Rate (mL/Sec) Study 1



* indicates significant difference from placebo (p-value ≤0.050).
B = Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0.
Subsequent values are observed cases.
LOCF = Last observation carried forward for patients not completing the 13-week study.
Note: The uroflowmetry assessments at Week 0 were recorded 4 to 8 hours after patients received the first dose of double-blind medication. Measurements at each visit were scheduled 4 to 8 hours after dosing (approximate peak plasma tamsulosin concentration).
Note: Patients in the 0.8 mg treatment groups received 0.4 mg for the first week.

Figure 3B Mean Increase in Peak Urine Flow Rate (mL/Sec) Study 2



* Indicates significant difference from placebo (p-value ≤0.050).
Baseline measurement was taken Week 0. Subsequent values are observed cases.
LOCF = Last observation carried forward for patients not completing the 13-week study.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Week 1 and Week 2 measurements were scheduled 4 to 8 hours after dosing (approximate peak plasma tamsulosin concentration). All other visits were scheduled 24 to 27 hours after dosing (approximate trough tamsulosin concentration).

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 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.

An increased incidence of proliferative alterations in the mammary glands of rat and mice females has been found. 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.

PRESENTATION

Urisolin 0.4mg Capsules are available in alu-alu blister pack of 10's.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight and reach of children.

REGISTRATION NUMBER

Urisolin 0.4mg Capsules: 083160

Manufacturing License No: 000647

Product Complies U.S.P. Dissolution Test II

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Mfg. U.S.P. Specs.

Manufactured by:

The Searle Company Limited,

32-Km, Multan Road, Lahore-Pakistan.

Marketed by:

IBL HealthCare Limited,

One IBL Centre, 2nd Floor, Plot # 1,

Block 7 & 8, D.M.C.H.S, Tipu Sultan Road,

Off Shahra-e-Faisal, Karachi - Pakistan.

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