# PRODUCT MONOGRAPH

**Pr APO-TAMSULOSIN CR**

Tamsulosin Hydrochloride

Controlled-Release Tablets, 0.4 mg

SELECTIVE ANTAGONIST OF
$ALPHA_{1A / 1D}$ ADRENORECEPTOR SUBTYPES
IN THE PROSTATE AND BLADDER

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**[Pr]APO-TAMSULOSIN CR**
Tamsulosin Hydrochloride

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Controlled release tablet 0.4 mg | none<br>*For a complete listing see Dosage Forms, Composition and Packaging section* |

### INDICATIONS AND CLINICAL USE

APO-TAMSULOSIN CR (tamsulosin hydrochloride) is indicated for the treatment of Lower Urinary Tract Symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

**Geriatrics (> *65* years of age):**
Tamsulosin hydrochloride has been found to be a safe and effective alpha1 adrenoceptor antagonist when administered at therapeutic doses (0.4 mg once daily) to patients over the age of 65 years.

**Pediatrics:**
APO-TAMSULOSIN CR is not indicated for use in children.
The effectiveness of tamsulosin in 161 pediatric patients (ages 2-16 years) with neuropathic bladder was not demonstrated (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

### CONTRAINDICATIONS

- APO-TAMSULOSIN CR (tamsulosin hydrochloride) is contraindicated in patients known to have hypersensitivity including drug induced angioedema to tamsulosin or any component of the APO-TAMSULOSIN CR controlled release formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

- APO-TAMSULOSIN CR (tamsulosin hydrochloride)should not be administered to patients using concomitant strong CYP3A4 inhibitors (e.g. ketoconazole) (see section Drug Interactions).

### WARNINGS AND PRECAUTIONS

**As with all $\alpha_1$-adrenoceptor 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**.

**Patients beginning treatment with tamsulosin hydrochloride should be cautioned to avoid situations where injury could result should syncope occur (see ADVERSE REACTIONS).**

**General**

Tamsulosin hydrochloride is not indicated for the treatment of hypertension.

**Drug-Drug Interactions**

- Tamsulosin is extensively metabolized, mainly be CYP3A4 and CYP2D6. APO-TAMSULOSIN CR should not be used in combination with strong inhibitors of CYP3A4 (e.g.,ketoconazole). APO-TAMSULOSIN CR should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terbinafine) inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers.
- APO-TAMSULOSIN CR should be used with caution in combination with cimetidine.
- APO-TAMSULOSIN CR should not be used in combination with other alpha adrenergic blocking agents.
- Caution is advised when alpha adrenergic blocking agents including APO-TAMSULOSIN CR are coadministered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.
- Caution should be exercised with concomitant administration of warfarin and APO-TAMSULOSIN CR

**See Drug Interactions**

**Carcinoma of the Prostate**

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated to rule out the presence of carcinoma of the prostate.

**Orthostatic Hypotension**

While syncope is the most severe orthostatic symptom of $\alpha_1$-adrenoceptor antagonists, other symptoms can occur (dizziness and postural hypotension). In a phase III, randomized, double-blind, placebo-controlled trial involving male patients treated once daily with either 0.4 mg tamsulosin hydrochloride (n=350) or placebo (n=356), both supine and standing blood pressure were monitored over the course of the 12 week treatment period. There was a small, clinically insignificant decrease from baseline in mean supine and standing systolic/diastolic BP in both treatment groups; the decrease in BP from baseline in the tamsulosin hydrochloride group (< 2 mmHg) was comparable to the placebo group (< 1.5 mmHg). There were no cases of orthostatic hypotension or syncope reported in either treatment group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with caution.

If hypotension occurs, the patient should be placed in the supine position and if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further therapy with tamsulosin hydrochloride.

**Hepatic**

The treatment of patients with severe hepatic impairment should be approached with caution as no studies have been conducted in this patient population. No dose adjustment is warranted in hepatic insufficiency.

**Renal**

The treatment of patients with severe renal impairment (creatinine clearance of <10mL/min) should be approached with caution, as these patients have not been studied.

**Intraoperative Floppy Iris Syndrome**

During cataract and/or glaucoma surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported during post-marketing surveillance in association with alpha-1 blocker therapy, including tamsulosin hydrochloride. Most reports to date were in patients taking tamsulosin hydrochloride when IFIS occurred, but in some cases, tamsulosin hydrochloride had been stopped prior to surgery. In most of these cases, tamsulosin hydrochloride had been stopped recently prior to surgery (2 to 14 days), but in a few cases, IFIS was reported after the patient had been off tamsulosin hydrochloride for a longer period. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. IFIS may increase the risk of eye complications during and after the operation. The benefit of stopping alpha-1 blocker therapy, including tamsulosin hydrochloride prior to cataract and/or glaucoma surgery has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer than 2 week period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract and/or glaucoma surgery is scheduled is not recommended.

## Reproduction

Ejaculation disorders have been observed in short and long term clinical studies with tamsulosin (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported in post marketing.

## Sulfa Allergy

In patients with sulfa allergy, allergic reaction to tamsulosin hydrochloride capsules has been rarely reported. If a patient reports a serious or life-threatening sulfa allergy, caution is warranted when administering tamsulosin hydrochloride.

## Special Populations

**Pregnant Women:** Tamsulosin hydrochloride is not indicated for use in women. Studies in pregnant rats and rabbits at daily doses of 300 and 50 mg/kg, respectively (30,000 and 5,000 times the anticipated human dose), revealed no evidence of harm to the fetus. There are no adequate data on the use of tamsulosin in pregnant women; therefore the potential risk from the use of tamsulosin during pregnancy in humans is unknown.

**Nursing Women:** Tamsulosin hydrochloride is not indicated for use in women.

**Pediatrics:** Tamsulosin hydrochloride is not indicated for use in children. Tamsulosin hydrochloride has been studied in 161 pediatric patients (ages 2 to 16 years) with an elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida). The effectiveness of tamsulosin in this pediatric population was not demonstrated. The most frequently reported adverse events (≥5%) were urinary tract infection, vomiting, nasopharyngitis, influenza, headache, and abdominal pain.

**Geriatrics (> 65 years of age)**: There were no pharmacokinetic studies conducted in geriatric patients with tamsulosin hydrochloride controlled-release tablets.. Cross-study comparisons of overall exposure (AUC) and half-life of tamsulosin hydrochloride capsules indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. However, tamsulosin hydrochloride capsules have been found to be a safe and effective $alpha_1$ adrenoreceptor antagonist when administered at therapeutic doses to patients over the age of 65 years.

**Gender Effects:** Tamsulosin hydrochloride is not indicated for use in women. Safety, effectiveness, and pharmacokinetics have not been evaluated in women.

## Monitoring and Laboratory Tests

No laboratory test interactions with tamsulosin hydrochloride are known. Treatment with tamsulosin hydrochloride for up to 3 months had no significant effect on prostate specific antigen (PSA).

## Information for the patient (See PART III: CONSUMER INFORMATION)

Patients should be advised not to crush or chew tamsulosin hydrochloride controlled-release tablets. These tablets are specially formulated to control the delivery of tamsulosin HCl to the blood stream.

There are no specific studies conducted with tamsulosin hydrochloride and the ability to drive vehicles or use machinery. However patients should be advised that dizziness can occur with tamsulosin hydrochloride, requiring caution in people who must drive, operate machinery, or perform hazardous tasks.

Patients should be advised about the possibility of priapism as a result of treatment with tamsulosin hydrochloride and other similar medications. Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction (impotence).

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Information on the safety profile of tamsulosin hydrochloride was derived from two, 3-month placebo-controlled clinical trials involving 1840 male subjects. Of these, 563 were treated with tamsulosin hydrochloride controlled-release tablets 0.4 mg,709 with tamsulosin hydrochloride capsules 0.4 mg and 568 with placebo. The results suggest that tamsulosin hydrochloride controlled-release tablets 0.4 mg and tamsulosin hydrochloride capsules 0.4 mg 0.4 mg were very well tolerated with the AE profile of tamsulosin hydrochloride controlled-release tablets 0.4 mg tending to be more favourable than that of tamsulosin hydrochloride capsules.

In these studies, 3.6% of patients taking tamsulosin hydrochloride controlled-release tablets (0.4 mg) discontinued from the study due to adverse events compared with 1.2% in the placebo group. The most frequently reported Treatment Emergent Adverse Events (TEAE) in the tamsulosin hydrochloride controlled-release tablets 0.4 mg group were dizziness and those related to abnormal ejaculation, although the incidence of both were comparable to placebo.

Impotence and other events related to sexual function are commonly associated with other alpha$_1$-blockers, however in the 3-month studies with tamsulosin hydrochloride controlled-release tablets there were minimal effects on sexual function and ejaculatory disorders/abnormalities with no reports of priapism. The difference in incidence of ejaculatory disorders/abnormalities between tamsulosin hydrochloride controlled-release tablets and placebo was not statistically significant. No patient discontinued treatment with tamsulosin hydrochloride controlled-release tablets 0.4 mg due to ejaculatory disorders/abnormalities.

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

**TABLE 1: TREATMENT-EMERGENT ADVERSE EVENTS IN ≥ 2% OF PATIENTS RECEIVING EITHER TAMSULOSIN OR PLACEBO DURING THE 3 MONTH PLACEBO AND ACTIVE-CONTROLLED STUDY.**

| **SOC/Preferred term** | **Placebo N=356** | **Tamsulosin Hydrochloride Controlled-Release Tablets 0.4 mg N=360** | **Tamsulosin Capsules 0.4 mg N=709** |
|---|---|---|---|
| Any TEAE | 71 (19.9%) | 93 (25.8%) | 168 (23.7%) |
| Cardiac disorders | 8 (2.2%) | 8 (2.2%) | 16 (2.3%) |
| Gastrointestinal disorders | 7 (2.0%) | 14 (3.9%) | 34 (4.8%) |
| General Disorders and administration site conditions | 2 (0.6%) | 8 (2.2%) | 11 (1.6%) |
| Infections and infestations | 16 (4.5%) | 20 (5.6%) | 32 (4.5%) |
| Investigations | 10 (2.8%) | 6 (1.7%) | 10 (1.4%) |
| Musculoskeletal and connective tissue disorders | 7 (2.0%) | 9 (2.5%) | 12* (1.7%) |
| Nervous system disorders | 9 (2.5%) | 11 (3.1%) | 29 (4.1%) |
| Reproductive system and breast disorders | 2 (0.6%) | 12 (3.3%) | 28 (3.9%) |
| Respiratory, thoracic and mediastinal disorders | 3 (0.8%) | 10 (2.8%) | 20 (2.8%) |
| Vascular disorders | 8 (2.2%) | 6[#] (1.7%) | 15 (2.1%) |

Number (%) of patients
A patient may experience an AE more than once or may experience more than one AE within the same SOC.
*Post database lock: deletion of 1 AE
[#]Post database lock: addition of 1 AE

**TABLE 2: NUMBER (%) OF PATIENTS WITH TEAES COMMONLY ASSOCIATED WITH $_{A1}$-AR ANTAGONISTS DURING THE 3 MONTH PLACEBO AND ACTIVE-CONTROLLED STUDY.**

| SOC/Preferred term | **Placebo N=356** | Tamsulosin Hydrochloride Controlled-Release **Tablets 0.4 mg N=360** | Tamsulosin Capsules 0.4 mg N=709 |
|---|---|---|---|
| **Non-cardiovascular class effects** | | | |
| Retrograde ejaculation | 1 (0.3%) | 6 (1.7%) | 10 (1.4%) |
| Ejaculation Failure | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) |
| Semen volume reduced | 0 (0.0%) | 1 (0.3%) | 2 (0.3%) |
| Ejaculation delayed | 0 (0.0%) | 1 (0.3%) | 2 (0.3%) |
| Ejaculation disorder NOS | 0 (0.0%) | 0 (0.0%) | 6 (0.8%) |
| ABNORMAL EJACULATION POOLED | 1 (0.3%) | 7 (1.9%) | 22 (3.1%) |

| | | | |
|---|---|---|---|
| Headache NOS | 4 (1.1%) | 3 (0.8%) | 10 (1.4%) |
| Asthenia | 1 (0.3%) | 1 (0.3%) | 1 (0.1%) |
| Fatigue | 1 (0.3%) | 3 (0.8%) | 2 (0.3%) |
| Somnolence | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) |
| Rhinitis NOS | 0 (0.0%) | 1 (0.3%) | 2 (0.3%) |
| Nasal congestion | 0 (0.0%) | 1 (0.3%) | 1 (0.1%) |
| Nasal obstruction | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Sub-Total | 7 (2.0%) | 16 (4.4%) | 36 (5.1%) |
| **Cardiovascular class effects** | | | |
| Dizziness | 5 (1.4%) | 5 (1.4%) | 9 (1.3%) |
| Dizziness aggravated | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) |
| Dizzy spell | 0 (0.0%) | 0 (0.0%) | 1 (0.1%) |
| DIZZINESS POOLED | 5 (1.4%) | 5 (1.4%) | 12 (1.7%) |
| Palpitations | 2 (0.6%) | 2 (0.6%) | 1 (0.1%) |
| Tachycardia NOS | 0 (0.0%) | 1 (0.3%) | 2 (0.3%) |
| Hypotension NOS | 1 (0.3%) | 0 (0.0%) | 2 (0.3%) |
| Orthostatic hypotension | 0 (0.0%) | 0 (0.0%) | 3 (0.4%) |
| Dizziness postural | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) |
| Syncope | 0 (0.0%) | 0 (0.0%) | 1 (0.1%) |
| Orthostatic/circulatory collapse | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Depressed level of/loss of consciousness | 0 (0.0%) | 1 (0.3%) | 1 (0.1%) |
| Sub-Total | 8 (2.2%) | 9 (2.5%) | 23 (3.2%) |
| TOTAL | 13 (3.7%) | 25 (6.9%) | 55 (7.8%) |

A patient may experience an AE more than once or may experience more than one AE within the same SOC.

Angioedema or priapism were not reported in the phase 2 or 3 studies.

## Post-Market Adverse Drug Reactions

The following adverse reactions have been reported during the use of tamsulosin hydrochloride at a frequency of:

>1% AND < 10%:
Nervous System Disorders: dizziness
Reproductive system and breast disorders: ejaculation disorders including retrograde ejaculation and ejaculation failure

> 0.1% AND < 1%:
Cardiac disorders: palpitations
Gastrointestinal Disorders: constipation, diarrhea, nausea, and vomiting
General disorders and administration site conditions: asthenia
Nervous systems disorders: headache
Respiratory, thoracic and mediastinal disorders: rhinitis
Skin and subcutaneous tissue disorders: rash, pruritus, urticaria
Vascular disorders: orthostatic hypotension

> 0.01% AND < 0.1%:
Nervous system disorders: syncope
Skin and subcutaneous system disorderd: angioedema

< 0.01%:
Reproductive systems and breast disorders:priapism
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

**Not Known (cannot be estimated from the available data)**

Eye disorders: vision blurred, visual impairment
Respiratory, thoracic and mediastinal disorders: epistaxis
Skin and subcutaneous tissue disorders: erythema multiforme, dermatitis exfoliative
Gastrointestinal Disorders: dry mouth

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.

During cataract and glaucoma surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported during post-marketing surveillance in association with alpha-1 blocker therapy, including tamsulosin hydrochloride (see **WARNINGS AND PRECAUTIONS**).

An open label extension study involving 609 male patients with lower urinary tract symptoms (LUTS) associated with BPH demonstrated sustained efficacy, safety and long-term tolerability of tamsulosin for up to 6 years.

## DRUG INTERACTIONS

### Overview

There were no drug interaction studies conducted specifically with tamsulosin hydrochloride controlled-release tablets and it is expected that the interaction profile would not be any different than that of tamsulosin hydrochloride capsules. As with tamsulosin hydrochloride capsules, caution should be exercised with concomitant administration of tamsulosin hydrochloride controlled-release tablets and other alpha-adrenergic blocking agents.

No clinically significant drug-drug interactions were observed when tamsulosin hydrochloride capsules 0.4 mg or 0.8 mg were administered with one of the following therapeutic agents: nifedipine, atenolol, enalapril, digoxin, furosemide or theophylline.

### Drug-Drug Interactions

### Strong and Moderate Inhibitors of CYP3A4 or CYP2D6

Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6.

The effects of ketoconazole (a strong inhibitor of CYP3A4) at 400 mg once daily for 5 days on the pharmacokinetics of a single tamsulosin capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range 23 to 47 years). Concomitant treatment with ketoconazole resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 2.2 and 2.8, respectively. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g., erythromycin) on the pharmacokinetics of tamsulosin have not been evaluated.

The effects of paroxetine (a strong inhibitor of CYP2D6) at 20 mg once daily for 9 days on the pharmacokinetics of a single tamsulosin capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range 23 to 47 years). Concomitant treatment with paroxetine resulted in an increase in the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). A fraction of the population (about 7% of Caucasians and 2% of African Americans) is CYP2D6 PMs. Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when tamsulosin is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). Tamsulosin should be given with caution in combination with moderate inhibitors of CYP3A4.

The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g., terbinafine) on the pharmacokinetics of tamsulosin have not been evaluated.

The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when it is co-administered with a combination of both CYP3A4 and CYP2D6 inhibitors.

**Nifedipine, Atenolol, Enalapril:** No dosage adjustments are necessary when tamsulosin hydrochloride controlled release tablets are administered concomitantly with nifedipine extended release tablets, atenolol, or enalapril. In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of nifedipine extended release tablets, atenolol or enalapril for at least three months, tamsulosin hydrochloride 0.4 mg capsules for seven days followed by tamsulosin hydrochloride 0.8 mg capsules for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study).

**Warfarin:** A definitive drug-drug interaction study between tamsulosin and warfarin was not conducted. Results from limited in-vitro and in-vivo studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

**Digoxin and Theophylline:** No dosage adjustments are necessary when tamsulosin hydrochloride is administered concomitantly with digoxin or theophylline. In two studies in healthy volunteers (n=10 per study; age range 19-39 years), receiving tamsulosin hydrochloride capsules 0.4 mg/day for two days, followed by tamsulosin hydrochloride capsules 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline.

**Furosemide:** No dosage adjustments are necessary when tamsulosin hydrochlorideis administered concomitantly with furosemide. The pharmacokinetic and pharmacodynamic interaction between tamsulosin hydrochloride capsules 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range 21-40 years). Tamsulosin hydrochloride capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced a 11% to 12% reduction in tamsulosin $C_{max}$ and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin hydrochloride controlled-release tablets dosage.

**PDE5 Inhibitors**

Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension. Therefore, caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors.

**Cimetidine:** The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single tamsulosin hydrochloride capsules 0.4 mg dose was investigated in ten healthy volunteers (age range 21-38 years). Treatment with cimetidine resulted in a moderate increase in tamsulosin AUC (44%) due to a significant decrease (26%) in the clearance of tamsulosin. Therefore, tamsulosin hydrochloride controlled-release tablets should be used with caution in combination with cimetidine.

**Other Alpha Adrenergic Blocking Agents**

The pharmacokinetic and pharmacodynamic interactions between tamsulosine and other alpha adrenergic blocking agents have not been determined; however, interactions between tamsulosine and other alpha adrenergic blocking agents may be expected.

**Drug-Laboratory Test Interactions**

No laboratory test interactions with tamsulosin hydrochlorideare known. Treatment with tamsulosin hydrochloride for up to 3 months had no significant effect on prostate specific antigen (PSA).

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

APO-TAMSULOSIN CR (tamsulosin hydrochloride) 0.4 mg once daily is recommended as the dose for the treatment of lower urinary tract symptoms (LUTS) associated with Benign Prostatic Hyperplasia (BPH).

**Missed Dose**

If a dose of APO-TAMSULOSIN CR is missed, the missed dose can be taken later the same day. If a day is missed, the missed dose should be skipped and the regular dosing schedule should be resumed. Doses must not be doubled.

**Administration**

APO-TAMSULOSIN CR should be taken at the same time each day with or without food. APO-TAMSULOSIN CR tablets **must be swallowed whole, as crushing or chewing will interfere with the controlled release of the active ingredient**.
Taking APO-TAMSULOSIN CR with a high fat meal increase exposure to tamsulosin (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics section)

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

Should overdosage of tamsulosin hydrochloride lead to hypotension, (see **WARNINGS AND PRECAUTIONS**), support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin is 94% to 99% protein bound: therefore dialysis is unlikely to be of benefit.

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.

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 was discharged the same day. One patient reported an overdose of 30 X 0.4 mg tamsulosin hydrochloride capsules. Following the ingestion of the capsules, the patient reported a headache judged to be severe and probably drug-related that resolved the same day.

## ACTION AND CLINICAL PHARMACOLOGY

**Mechanism of Action**

Tamsulosin hydrochloride is an $alpha_1$ adrenoreceptor (AR) blocking agent used for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). It exhibits selectivity for both $alpha_{1A}$ and $alpha_{1D}$ receptors over the $alpha_{1B}$ AR subtype. These three AR subtypes have a distinct distribution pattern in human tissue.Whereas approximately 70% of the $alpha_1$-receptors in human prostate are of the $alpha_{1A}$ subtype, the human bladder contains predominantly the $alpha_{1D}$ subtype while blood vessels express predominantly $alpha_{1B}$ subtype.

Stimulation/antagonism of each of the receptor subtypes gives rise to a distinct pharmacological effect.

Lower Urinary Tract Symptoms (LUTS) suggestive of benign prostatic obstruction (BPO) formerly referred to as symptomatic benign prostatic hyperplasia (BPH) are very common in men > 50 years old; the prevalence increases with age. The symptoms associated with LUTS/BPH are comprised of two underlying components: the static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of $alpha_1$ adrenoreceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoreceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.

It is further believed that blockade of $alpha_{1D}$ subtypes in the human obstructed bladder may be responsible for reducing detrusor overactivity and subsequent relief of storage symptoms.

Tamsulosin hydrochloride is not intended for use as an antihypertensive drug.

**Pharmacodynamics**

The pharmacokinetics of tamsulosin have been evaluated in adult healthy volunteers with doses ranging from 0.4 mg to 1.6 mg.

**Pharmacokinetics**

Absorption: After a single oral dose of 0.4 mg of tamsulosin hydrochloride controlled-release tablets in the fasted state, the plasma concentration of tamsulosin gradually increased reaching $C_{max}$ at a median time of 6 hours. At steady state, which is reached by day 4 of multiple dosing, plasma concentrations of tamsulosin peak at 4-6 hours in the fasted and fed state. Peak plasma concentrations increase from approximately 6 ng/mL after the first dose to 11 ng/mL in steady state. After $C_{max}$ is reached, the plasma concentration decreases, but at approximately 16-24 hours post-dose, a small increase or second plateau is observed. The absolute bioavailability of tamsulosin from tamsulosin hydrochloride controlled-release tablets was estimated to be 55-59%.

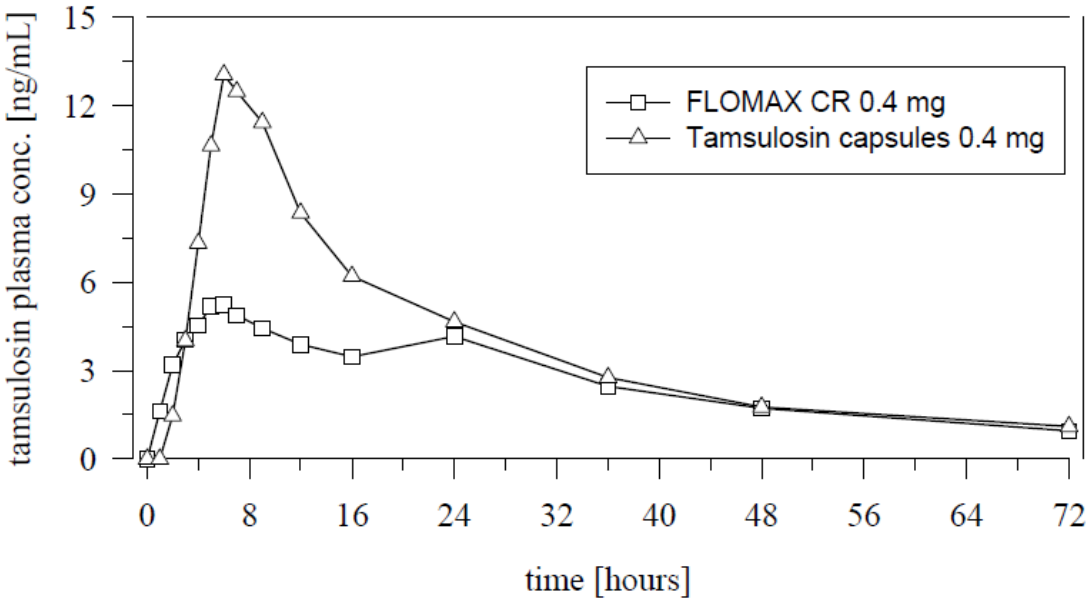
A study conducted at steady state with 0.4 mg tamsulosin hydrochloride controlled-release tablets demonstrated that the plasma concentration-time profile in the fed state was bioequivalent to the fasted state, indicating the absence of a food effect by a low fat meal (Table 3). After a single oral dose of 0.4mg , tamsulosin hydrochloride controlled-release the extent of absorption is increased by 64% and 149% (AUC and Cmax respectively) by a high-fat meal compared to fasted.

**Table 3: MEAN PHARMACOKINETIC PARAMETERS OF TAMSULOSIN AT STEADY STATE FOLLOWING ADMINISTRATION OF ONCE DAILY DOSES OF 0.4 MG TAMSULOSIN HYDROCHLORIDE CONTROLLED-RELEASE TABLETS IN BOTH THE FED AND FASTED STATE.**

| Parameter | Tamsulosin Hydrochloride Controlled-Release Tablets 0.4 mg (Fed) (n=24) | Tamsulosin Hydrochloride Controlled-Release Tablets 0.4 mg (Fasted) (n=24) |
|---|---|---|
| $AUC_{0\text{-}inf}$ (ng·h/mL) | 291.1 | 278.7 |
| $C_{max}$ (ng/mL) | 11.1 | 10.7 |
| $C_{24}$ (ng/mL) | 4.8 | 4.6 |
| $T_{max}$ (h) | 4.16 | 4.75 |
| $T_{½}$ (h) | 14.6 | 15.6 |

The 0.4 mg tamsulosin hydrochloride controlled-release tablet is not bioequivalent to the 0.4 mg tamsulosin hydrochloride capsule, as the test/reference ratio for $C_{max}$ and AUC did not fall within the predefined limits of 80-125%. The plasma concentration-time profile presented in Figure 1 shows the lack of a pronounced spike in $C_{max}$ with tamsulosin hydrochloride controlled-release tablets compared with capsules which may be consistent with a more favourable safety profile.

**FIGURE 1: MEAN TAMSULOSIN PLASMA VS. TIME PROFILES OF TAMSULOSIN HYDROCHLORIDE CONTROLLED-RELEASE TABLETS 0.4 MG AND TAMSULOSIN CAPSULES, 0.4 MG (N=12)**




**Distribution:** The mean steady-state apparent volume of distribution of tamsulosin after intravenous administration to ten healthy male adults was 16 litres, which is suggestive of distribution into extracellular fluids in the body. Additionally, whole body autoradiographic studies in mice, rats and dogs indicate that tamsulosin is widely distributed to most tissues including kidney, prostate, liver, gall bladder, heart, aorta, and brown fat, and minimally distributed to the brain, spinal cord, and testes.

Tamsulosin is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1-acid glycoprotein (AAG) in humans, with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin had no effect on the extent of binding of these drugs.

**Metabolism:** Tamsulosin is extensively metabolized by cytochrome P450 enzymes (CYP3A) in the liver, followed by extensive glucuronide or sulfate conjugation of metabolites. On administration of a dose of radiolabelled tamsulosin to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours. Less than 10% of the dose was recovered as unchanged (parent) compound in the urine.

Metabolites of tamsulosin do not contribute significantly to tamsulosin adrenoreceptor antagonist activity. Furthermore, there is no enantiomeric bioconversion from tamsulosin [R(-) isomer] to the S(+) isomer in studies with mice, rats, dogs, and humans.

Incubations with human liver microsomes showed no evidence of clinically significant interactions between tamsulosin and drugs which are known to interact or be metabolized by hepatic enzymes, such as amitriptyline, diclofenac, albuterol (beta agonist), glyburide (glibenclamide), finasteride (5 alpha-reductase inhibitor for treatment of BPH), and warfarin. No dose adjustment is warranted in hepatic insufficiency.

**Excretion:** Tamsulosin undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h). Tamsulosin exhibits linear pharmacokinetics following single or multiple dosing of tamsulosin hydrochloride controlled-release tablets resulting in a proportional increase in $C_{max}$ and AUC with increasing doses. Intrinsic clearance is independent of tamsulosin binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin in plasma ranged from five to seven hours. Because of absorption rate-controlled pharmacokinetics with the tamsulosin hydrochloride controlled-release tablets formulation, the apparent half-life of tamsulosin increases to approximately 12 to 15 hours in healthy volunteers.

**Special Populations and Conditions**

**Pediatrics**: Tamsulosin hydrochloride is not indicated for use in children. The effectiveness of tamsulosin in children (ages 2 to 16 years) with neuropathic bladder was not demonstrated (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics). Pharmacokinetics have not been evaluated in pediatrics.

**Geriatrics**: There were no pharmacokinetic studies conducted in geriatric patients with tamsulosin hydrochloride controlled-release tablets. Cross-study comparisons of overall exposure (AUC) and half-life of tamsulosin hydrochloride capsules indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. However, tamsulosin hydrochloride capsules have been found to be a safe and effective $alpha_1$ adrenoreceptor antagonist when administered at therapeutic doses to patients over the age of 65 years.

**Gender Effects:** Tamsulosin hydrochloride is not indicated for use in women. Pharmacokinetics have not been evaluated in women.

**Hepatic Insufficiency:** The pharmacokinetics of tamsulosin have been compared in subjects with hepatic dysfunction (n=8) and in normal subjects (n=8). While a change in the overall plasma concentration of tamsulosin was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin. Therefore, patients with mild to moderate hepatic dysfunction do not require an adjustment in tamsulosin hydrochloride dosage.

**Renal Insufficiency:** The pharmacokinetics of tamsulosin have been compared in subjects with moderate (n=6) or severe (n=6) renal impairment and in normal subjects (n=6). While a change in the overall plasma concentration of tamsulosin was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with such renal impairment do not require an adjustment in tamsulosin hydrochloride dosing. Patients with end stage renal disease ($Cl_{cr}$ <10mL/min) have not been studied.

## STORAGE AND STABILITY

Store at room temperature (15-30ºC).

## DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-TAMSULOSIN CR Tablets 0.4 mg: Each yellowish-brown, round, biconvex film-coated tablet, engraved "TA" over "0.4" on one side, "APO" on the other side contains 0.4 mg of tamsulosin hydrochloride. Available in HDPE bottles of 100 and 500 tablets and blister packs of 100 tablets.

In addition to tamsulosin hydrochloride, each tablet also contains the following **non-medicinal ingredients** (in alphabetical order): citric acid, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2208 and 2910, magnesium stearate, polyethylene glycol, sodium alginate and yellow ferric oxide.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

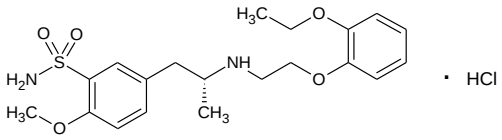
### Drug Substance

Proper name: Tamsulosin hydrochloride

Chemical name: 5-[(2R)-2-{[2-(2-ethoxyphenoxy)ethyl]amino}propyl]-2-methoxybenzenesulfonamide hydrochloride.

Molecular formula and molecular mass: $C_{20}H_{28}N_2O_5S \cdot HCl$; 444.97

Structural Formula:




Physicochemical properties:

Tamsulosin HCl is a white to almost white solid. Slightly soluble in water, freely soluble in formic acid, slightly soluble in anhydrous ethanol.

pH: 5.34 (1% aqueous solution)

pKa: 8.4 (secondary amine); 10.2 (sulfonamide)

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions was performed on healthy male volunteers. The rate and extent of absorption of tamsulosin was measured and compared following a single oral dose (1 x 0.4 mg tablet) of Flomax® CR (tamsulosin hydrochloride) and Apo-Tamsulosin (tamsulosin hydrochloride) in 30 volunteers. The results from measured data are summarized in the following table:

Summary Table of the Comparative Bioavailability Data
Tamsulosin
(A single 0.4 mg dose: 1 x 0.4 mg)
From Measured Data/Fasting Conditions
Geometric Mean
Arithmetic Mean (CV%)

| Parameter | Apo–Tamsulosin (Apotex Inc.) (Canada) | Flomax® CR† (Boehringer Ingelheim (Canada) Ltd.) (Canada) | Ratio of Geometric Means (%) | 90% Confidence Interval (%) |
|---|---|---|---|---|
| $AUC_t$ (ng•h/mL) | 96.471<br>110.617 (50) | 94.411<br>110.257 (56) | 102.2 | 91.9 – 113.6 |
| $AUC_{inf}$ (ng•h/mL) | 103.299<br>119.182 (47) | 102.177<br>124.844 (59) | 101.1 | 88.9 – 114.9 |
| $C_{max}$ (ng/mL) | 5.273<br>5.586 (33) | 4.786<br>5.061 (35) | 110.2 | 99.4 – 122.1 |
| $T_{max}$§ (h) | 5.34 (60) | 4.60 (30) | | |
| $T_{half}$§ (h) | 12.97 (28) | 14.60 (45) | | |

For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

§ Arithmetic means (CV%) only.

† Flomax® CR is manufactured by Boehringer Ingelheim (Canada) Ltd. and was purchased in Canada.

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions was performed on healthy male volunteers. The rate and extent of absorption of tamsulosin was measured and compared following a single oral dose (1 x 0.4 mg tablet) of Flomax® CR (tamsulosin hydrochloride) and Apo-Tamsulosin (tamsulosin hydrochloride) in 18 volunteers. The results from measured data are summarized in the following table:

Summary Table of the Comparative Bioavailability Data
Tamsulosin
(A single 0.4 mg dose: 1 x 0.4 mg tablet)
From Measured Data/Fed Conditions
Geometric Mean
Arithmetic Mean (CV%)

| Parameter | Apo–Tamsulosin (Apotex Inc.) (Canada) | Flomax® CR † (Boehringer Ingelheim (Canada) Ltd.) (Canada) | Ratio of Geometric Means (%) | 90% Confidence Interval (%) |
|---|---|---|---|---|
| $AUC_t$ (ng•h/mL) | 140.116<br>148.673 (36) | 145.742<br>158.189 (42) | 96.1 | 83.9 – 110.2 |
| $AUC_{inf}$ (ng•h/mL) | 147.466<br>156.057 (35) | 152.511<br>164.811 (41) | 96.7 | 84.9 – 110.1 |
| $C_{max}$ (ng/mL) | 7.266<br>7.550 (28) | 8.576<br>9.198 (41) | 84.7 | 75.4 – 95.2 |
| $T_{max§}$ (h) | 6.44 (46) | 6.78 (33) | | |
| $T_{half§}$ (h) | 13.41 (35) | 13.28 (33) | | |

For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

§ Arithmetic means (CV%) only.

† Flomax® CR is manufactured by Boehringer Ingelheim (Canada) Ltd. and was purchased in Canada.

A randomized, multiple dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions at steady state was performed on healthy male volunteers. The rate and extent of absorption of tamsulosin was measured and compared following a multiple oral dose (7 x 0.4 mg tablet) of Flomax® CR (tamsulosin hydrochloride) and Apo-Tamsulosin (tamsulosin hydrochloride) in 33 volunteers. The results from measured data are summarized in the following table:

Summary Table of the Comparative Bioavailability Data
Tamsulosin
(A Multiple 0.4 mg dose: 7 x 0.4 mg)
From Measured Data/Fasting Conditions at Steady State
Geometric Mean
Arithmetic Mean (CV%)

| Parameter | Apo–Tamsulosin (Apotex Inc.) (Canada) | Flomax® CR† (Boehringer Ingelheim (Canada) Ltd.) (Canada) | Ratio of Geometric Means (%) | 90% Confidence Interval (%) |
|---|---|---|---|---|
| $AUC_{tau}$ (ng•h/mL) | 101.810<br>109.924 (41) | 110.651<br>128.335 (61) | 92.0 | 83.2 – 101.8 |
| $C_{max}$ (ng/mL) | 7.988<br>8.382 (32) | 8.111<br>9.019 (51) | 98.5 | 90.3 – 107.4 |
| $C_{min}$ (ng/mL) | 2.048<br>2.417 (61) | 2.474<br>3.142 (75) | 82.8 | 70.9 – 96.7 |
| $T_{max}$§ (h) | 3.82 (25) | 4.52 (24) | | |
| Fluc§ (%) | 140.78 (30) | 123.83 (38) | | |

For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).
§ Arithmetic means (CV%) only.
† Flomax® CR is manufactured by Boehringer Ingelheim (Canada) Ltd. and was purchased in Canada.

## Other Studies

## Study demographics and trial design

Efficacy of tamsulosin hydrochloride controlled-release tablets has been evaluated in two double-blind, randomized, placebo controlled studies of 12-weeks duration involving a total of 1840 male subjects. Of these, 563 were treated with tamsulosin hydrochloride controlled-release tablets 0.4 mg, 709 with tamsulosin hydrochloride capsules 0.4 mg and 568 with placebo. The main inclusion criteria in both trials were: male patients aged $\geq 45$ years with symptoms diagnosed as LUTS suggestive of BPH. These patients had to have a total International Prostate Symptom Score (I-PSS) of $\geq 13$ at enrollment and after 2 week placebo run-in. In both studies, tamsulosin (or placebo) was orally administered at the specified dosage once daily.

The primary efficacy parameter for both studies was the change from baseline to endpoint in Total I-PSS for the full analysis set (FAS). The I-PSS consists of questions that assess the severity of both irritative and obstructive symptoms, with possible scores ranging from 0 to 35. The secondary efficacy analysis contained the changes from baseline in voiding and storage I-PSS subscores, I-PSS QoL score and the individual I-PSS items.

**TABLE 4: EFFECT ON TOTAL I-PSS IN THE 3- MONTH STUDIES**

| **Study** | **Treatment Arm** | **No. Baseline/ Endpoint** | **Baseline Mean (SD)** | **Endpoint Mean (SD)** | **Change at Endpoint Mean (SD) [%]** | **Difference vs. Placebo Mean (95% CI)** | **P-value vs. Placebo** |
|---|---|---|---|---|---|---|---|
| 617-CL-303 | Placebo | 210[a]/211 | 17.8 (4.0) | 11.7 (6.1) | -6.0 (5.4) [-34.5] | - | |
| | Tamsulosin Hydrochloride Controlled-Release tablets 0.4 mg | 203/203 | 18.0 (4.3) | 10.4 (5.5) | -7.6 (5.3) [-42.4] | -1.6 (-2.5, -0.6) | 0.0016 |
| 617-CL-307 | Placebo | 350/350 | 18.3 (4.5) | 12.4 (6.4) | -5.8 (5.6) [-32.0] | - | - |
| | Tamsulosin Hydrochloride Controlled-Release tablets 0.4 mg | 354/354 | 18.5 (4.4) | 10.8 (6.2) | -7.7 (5.8) [41.7] | -1.7 (-2.5, -1.0) | <0.0001 |
| | Tamsulosin Capsules 0.4 mg | 700/700 | 18.5 (4.5) | 10.6 (5.9) | -8.0 (5.6)[-43.2] | -2.0 (-2.6,-1.3) | <0.0001 |

[a] Patient 1607 in the placebo group did not have an I-PSS at baseline (Visit 2) and the Visit 1 I-PSS of this patient was not included in the mean (SD) at baseline

**FIGURE 2: MEAN CHANGE FROM BASELINE IN TOTAL I-PSS OVER TIME IN THE PLACEBO CONTROLLED STUDY**

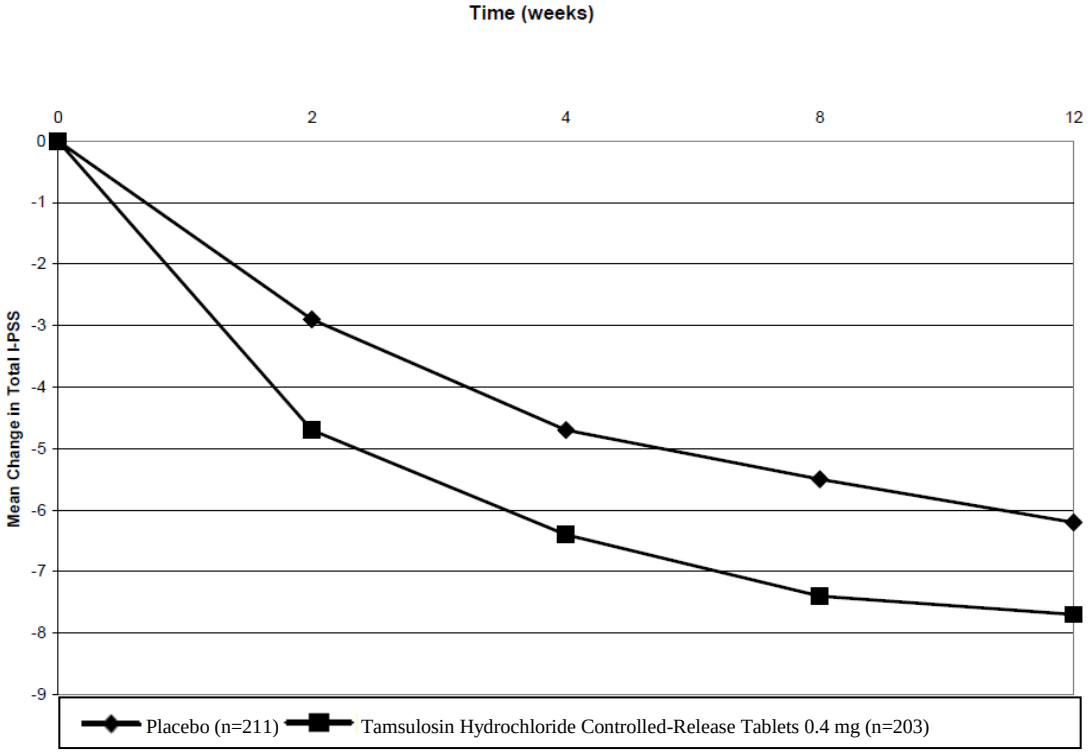
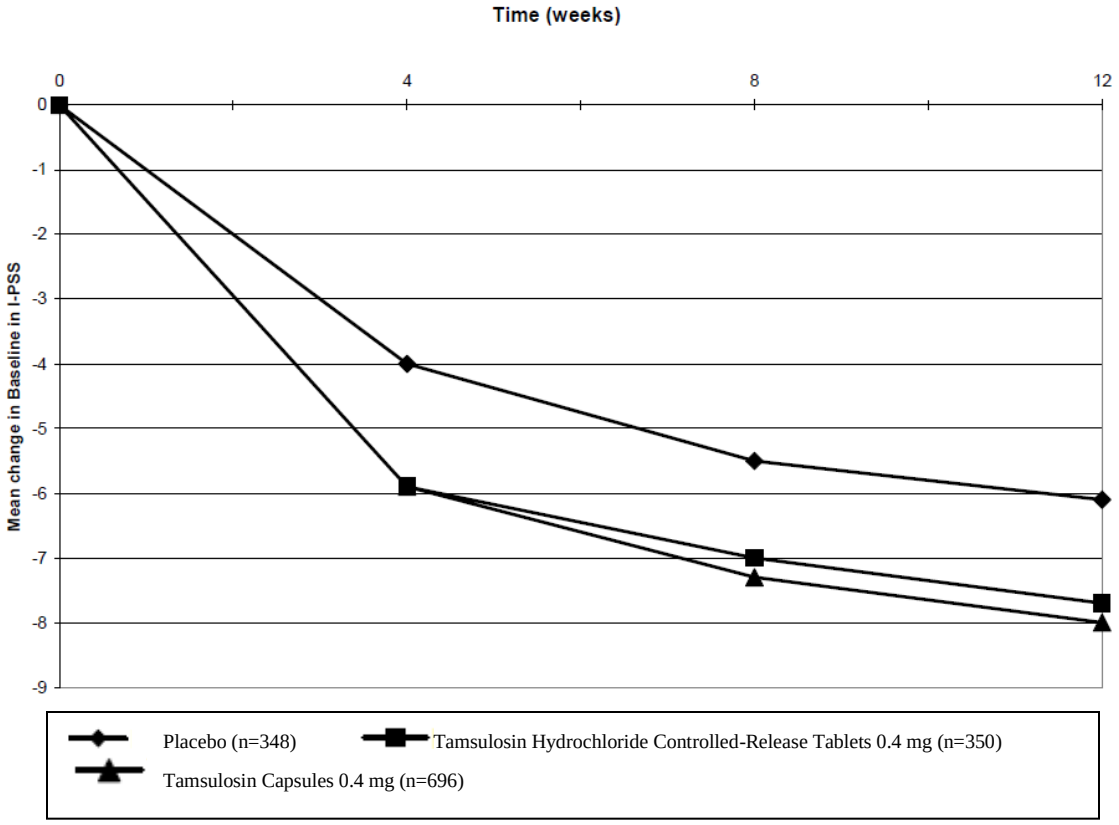


**FIGURE 3: MEAN CHANGE FROM BASELINE IN TOTAL I-PSS OVER TIME IN THE PLACEBO AND ACTIVE-CONTROLLED STUDY**




In both studies, tamsulosin hydrochloride controlled-release tablets 0.4 mg had a fast onset of action with decrease in I-PSS at 2-4 weeks. As evident from Table 4 and Figures 2 and 3, there was a statistically significant reduction ($p<0.001$) in the I-PSS vs. placebo in both studies indicating a reduction in symptom severity. This was due to a statistically significant improvement in both the irritative and obstructive subscores. Tamsulosin hydrochloride controlled-release tablets 0.4 mg was an efficacious dose and provided a response which was equivalent to that of tamsulosin hydrochloride 0.4 mg capsules confirming the recommendation of once daily dosing of 0.4 mg.

## DETAILED PHARMACOLOGY

See ACTION AND CLINICAL PHARMACOLOGY section

## TOXICOLOGY

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumour incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses ≥ 5.4 mg/kg ($P<0.015$). The highest doses of tamsulosin evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving doses of 0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumour findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P<0.0001$) and adenocarcinomas ($P<0.0075$). The highest dose levels of tamsulosin evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving doses of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin-induced hyperprolactinemia. It is not known if tamsulosin hydrochloride elevates prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is not known.

Tamsulosin produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin (AUC exposure in rats about 50 times the human exposure at a dose of 0.8 mg/day). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin (1/5 and 16 times the anticipated human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin on sperm counts or sperm function have not been evaluated.

Studies in female rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin, respectively. In female rats, the reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.