PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-TAMSULOSIN CR

Tamsulosin Hydrochloride Controlled-Release Tablets
Controlled Release Tablets, 0.4 mg, Oral
Apotex Standard

Selective Antagonist of
$Alpha_{1A / 1D}$ Adrenoreceptor subtypes
In the prostate and bladder

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	07/2024

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-TAMSULOSIN CR (tamsulosin hydrochloride controlled-release tablets) is indicated for:

- the treatment of Lower Urinary Tract Symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

1.1 Pediatrics (<16 years of age):

APO-TAMSULOSIN CR is not indicated for use in children.

The effectiveness of tamsulosin in 161 pediatric patients (ages 2 to 16 years) with neuropathic bladder was not demonstrated (see 7.1.3 Pediatrics).

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of tamsulosin hydrochloride controlled-release tablets in pediatric patients (ages 2 to 16 years) has not been established; therefore, Health Canada has not authorized an indication for pediatric use."

1.2 Geriatrics

Geriatrics (*> 65* years of age): Tamsulosin hydrochloride controlled-release tablets has been found to be a safe and effective alpha$_1$ adrenoceptor antagonist when administered at therapeutic doses (0.4 mg once daily) to patients over the age of 65 years.

2 CONTRAINDICATIONS

- APO-TAMSULOSIN CR (tamsulosin hydrochloride controlled-release tablets) 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.
- APO-TAMSULOSIN CR should not be administered to patients using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole) (see section 9 DRUG INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

APO-TAMSULOSIN CR 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).

4.4 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 10.3 Pharmacokinetics).

Information for the patient (See PATIENT MEDICATION 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 hydrochloride to the blood stream.

4.5 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.

5 OVERDOSAGE

Overdosage with APO-TAMSULOSIN CR can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosage.

Should overdosage of APO-TAMSULOSIN CR lead to hypotensive effects (see 7 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 of tamsulosin hydrochloride controlled-release tablets 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. 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Controlled release tablet 0.4 mg /corresponding to 0.4mg of tamsulosin HCl	Citric acid, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2208 and 2910, magnesium stearate, polyethylene glycol, sodium alginate, and yellow ferric oxide

APO-TAMSULOSIN CR Tablets 0.4 mg: Each yellowish-brown, round, biconvex film-coated tablet, engraved "TA" over "0.4" on one side, and plain on the other side contains 0.4 mg of tamsulosin hydrochloride. Available in HDPE bottles of 100 and 500 tablets and blister packs of 30 and 100 tablets.

7 WARNINGS AND PRECAUTIONS

As with all α_1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with APO-TAMSULOSIN CR, 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 APO-TAMSULOSIN CR should be cautioned to avoid situations where injury could result should syncope occur (see 8 ADVERSE REACTIONS).

General

APO-TAMSULOSIN CR is not indicated for the treatment of hypertension.

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.

Driving and Operating Machinery

There are no specific studies conducted with tamsulosin hydrochloride controlled-release tablets and the ability to drive vehicles or use machinery. However, patients should be advised that dizziness can occur with tamsulosin hydrochloride controlled-release tablets, requiring

caution in people who must drive, operate machinery, or perform hazardous tasks.

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 co-administered 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 9 DRUG INTERACTIONS

Hepatic/Biliary/Pancreatic

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.

Monitoring and Laboratory Tests

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

Ophthalmologic

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 controlled-release tablets. Most reports to date were in patients taking tamsulosin hydrochloride controlled-release tablets when IFIS occurred, but in some cases, tamsulosin hydrochloride

controlled-release tablets had been stopped prior to surgery. In most of these cases, tamsulosin hydrochloride controlled-release tablets 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 controlled-release tablets 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 controlled-release tablets in patients who had discontinued tamsulosin for a longer than 2 week period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride controlled-release tablets in patients for whom cataract and/or glaucoma surgery is scheduled is not recommended.

Orthostatic Hypotension

While syncope is the most severe orthostatic symptom of α_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 controlled-release tablets (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 controlled-release tablets 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 controlled-release tablets.

Renal

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.

Reproductive Health: Female and Male Potential

- **Function**

Ejaculation disorders have been observed in short and long term clinical studies with tamsulosin (see 8.2 Clinical Trial Adverse Reactions). Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported in post marketing.

Patients should be advised about the possibility of priapism as a result of treatment with tamsulosin hydrochloride controlled-release tablets 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).

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

Sensitivity/Resistance

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 controlled-release tablets.

7.1 Special Populations

7.1.1 Pregnant Women

Tamsulosin hydrochloride controlled-release tablets 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.

7.1.2 Breast-feeding
Tamsulosin hydrochloride controlled-release tablets is not indicated for use in women.

7.1.3 Pediatrics

Tamsulosin hydrochloride controlled-release tablets 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.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following clinically significant adverse effects may be associated with the treatment of APO-TAMSULOSIN CR (see 7 WARNINGS AND PRECAUTIONS):

- Intraoperative floppy iris syndrome (IFIS)
- Orthostatic hypotension
- Priapism

8.2 Clinical Trial Adverse 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.

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 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 was dizziness and those related to abnormal ejaculation, although the incidence of both was 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.

TABLE 2: 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 3: 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 was not reported in the phase 2 or 3 studies.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during the use of tamsulosin hydrochloride controlled-release tablets 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 tissue disorders: 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, tamsulosin-induced photosensitivity reaction
Gastrointestinal Disorders: dry mouth
General disorders and administration site conditions: chest discomfort

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 controlled-

release tablets (see 7 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.

9 DRUG INTERACTIONS

9.2 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.

9.4 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 C_{max} 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 hydrochloride controlled-release tablets 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 C_{max} 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 hydrochloride controlled-release tablets is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin hydrochloride controlled-release tablets should not be used in combination with strong

inhibitors of CYP3A4 (e.g., ketoconazole). Tamsulosin hydrochloride controlled-release tablets 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 hydrochloride controlled-release tablets have not been evaluated.

The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin hydrochloride controlled-release tablets have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when tamsulosin hydrochloride controlled-release tablets 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 to 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 controlled-release tablets.

Digoxin and Theophylline: No dosage adjustments are necessary when tamsulosin hydrochloride controlled-release tablets is administered concomitantly with digoxin or theophylline. In two studies in healthy volunteers (n=10 per study; age range 19 to 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 hydrochloride controlled-release tablets is 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 to 40 years). Tamsulosin hydrochloride capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 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.

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 to 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.

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 hydrochloride controlled-release tablets are co-administered with PDE5 inhibitors.

Other Alpha-Adrenergic Blocking Agents
The pharmacokinetic and pharmacodynamic interactions between tamsulosin hydrochloride controlled-release tablets and other alpha adrenergic blocking agents have not been determined; however, interactions between tamsulosin and other alpha adrenergic blocking agents may be expected.

Table 4 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Cimetidine	CT[1]	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 0.4 mg capsules 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.	Tamsulosin hydrochloride controlled-release tablets should be used with caution in combination with cimetidine.
Ketoconazole	CT[2]	Coadministration of ketoconazole increased the C_{max} and AUC from time zero to infinity (AUC_{∞}) of tamsulosin by 2.2- and 2.8-fold, respectively.	Tamsulosin hydrochloride controlled-release tablets should not be given in combination with strong inhibitors of CYP3A4.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Paroxetine	CT [2]	Coadministration of paroxetine increased the C_{max} and AUC_{∞} of tamsulosin by factors of approximately 1.3 and 1.6, respectively.	Increases in C_{max} and AUC of tamsulosin hydrochloride controlled-release tablets are not considered clinically relevant.
α_1-adrenoceptor antagonists	T [3,4]	Concurrent administration of other α_1-adrenoceptor antagonists could lead to hypotensive effects.	Tamsulosin hydrochloride controlled-release tablets should not be used in combination with other alpha adrenergic blocking agents.
Digoxin or Theophylline	CT [3,5]	Concurrent administration of digoxin with tamsulosin did not produce any change in the pharmacokinetics of digoxin or theophylline.	No adjustment in tamsulosin hydrochloride controlled-release tablets dosing is required when it is administered concomitantly with digoxin or theophylline.
PDE5 Inhibitors	CT	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 is advised when alpha adrenergic blocking agents including tamsulosin hydrochloride controlled-release tablets are co- administered with PDE5 inhibitors.
Antihypertensives (e.g., nifedipine, enalapril, and atenolol)	CT [6]	Tamsulosin hydrochloride controlled-release tablets did not interfere with or potentiate the antihypertensive action of nifedipine, enalapril, or atenolol. There was no alteration in drug trough levels with the concomitant administration of tamsulosin.	The dose of nifedipine, enalapril, or atenolol did not require adjustment in patients on which tamsulosin hydrochloride controlled-release tablets was given.
Erythromycin	T [7]	Erythromycin is a moderate inhibitor of CYP3A.	Tamsulosin hydrochloride controlled-release tablets should be used with caution in combination

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
			with moderate inhibitors of CYP3A4.
Furosemide	CT[8]	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 an 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 dosage.	No dosage adjustments are necessary when tamsulosin hydrochloride controlled-release tablets is administered concomitantly with furosemide.

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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.

APO-TAMSULOSIN CR is not intended for use as an antihypertensive drug.

10.2 Pharmacodynamics

APO-TAMSULOSIN CR (tamsulosin hydrochloride) 0.4 mg is a controlled-release tablet designed to provide a consistent slow release of tamsulosin which is maintained throughout the gastro-intestinal tract, resulting in an adequate exposure, with little fluctuation, over 24 hours.

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

10.3 Pharmacokinetics

Absorption: After a single oral dose of 0.4 mg 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 to 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 to 24 hours post-dose, a small increase or second plateau is observed. Under fasted conditions the absolute bioavailability of tamsulosin from tamsulosin hydrochloride controlled-release tablets was estimated to be 57%.

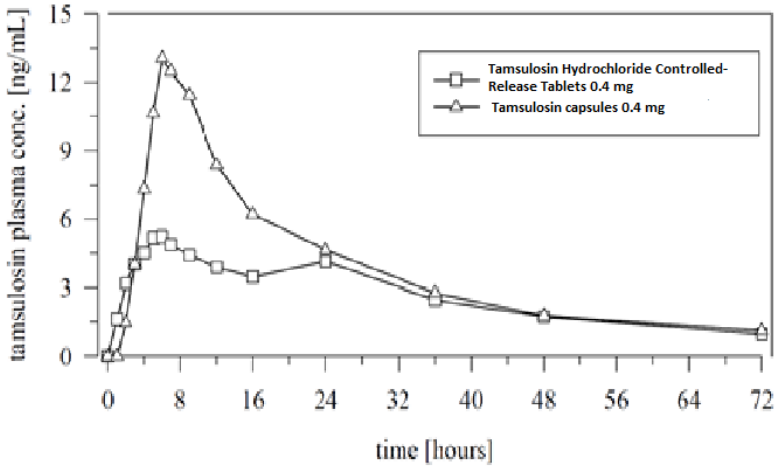
A study conducted at steady state with 0.4 mg tamsulosin hydrochloride controlled-release tablets demonstrated that the plasma concentration-time profile in the fed state was bioequivalent to the fasted state, indicating the absence of a food effect, by a low fat meal (Table 5). After a single oral dose of 0.4 mg tamsulosin hydrochloride controlled-release tablets, the extent of absorption is increased by 64% and 149% (AUC and C_{max} respectively) by a high-fat meal compared to fasted.

Table 5: 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 to 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 (CYP3A4 and CYP2D6) 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.

Elimination: 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 7.1.3 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.

- **Sex:** APO-TAMSULOSIN CR is not indicated for use in women. Pharmacokinetics has 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} <10 mL/min) have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

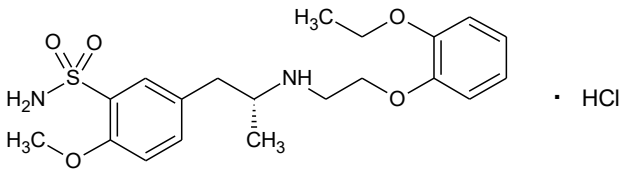
Drug Substance

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 g/mol

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)

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Lower Urinary Tract Symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)

Table 6 - Summary of patient demographics for clinical trials in Lower Urinary Tract Symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
617-CL-303	Double-blind, randomized,	Tamsulosin Hydrochloride	Tamsulosin Hydrochloride	≥ 45	males

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
	placebo controlled	Controlled-Release tablets 0.4 mg oral, Placebo, oral 12- weeks	Controlled-Release tablets 0.4mg (203) Placebo (211)		
617-CL-307	Double-blind, randomized, placebo controlled	Tamsulosin Hydrochloride Controlled-Release tablets 0.4 mg oral, Tamsulosin capsules 0.4 mg, oral, 12-weeks Placebo, oral 12 weeks	Tamsulosin Hydrochloride Controlled-Release tablets 0.4mg (354) Tamsulosin capsules (700) Placebo (350)	≥ 45	males

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 ≥ 45 years with symptoms diagnosed as LUTS suggestive of BPH. These patients had to have a total International Prostate Symptom Score (I-PSS) of ≥ 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 7: 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

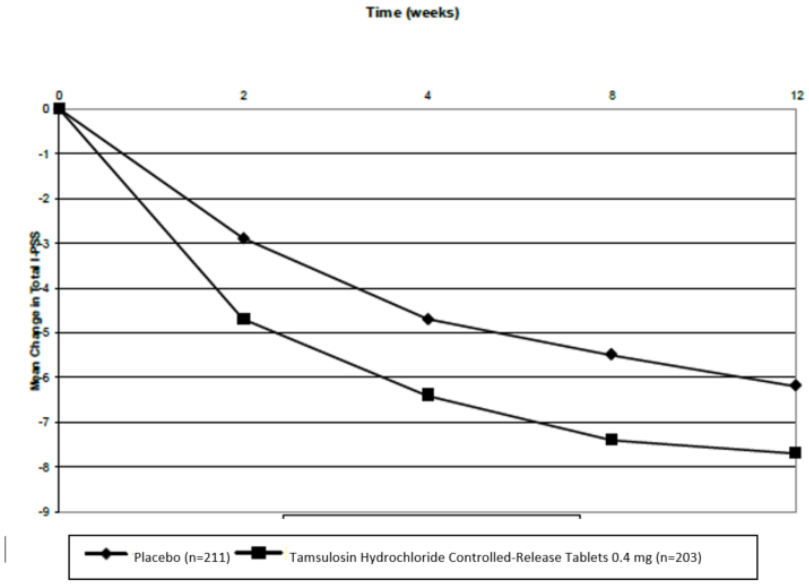
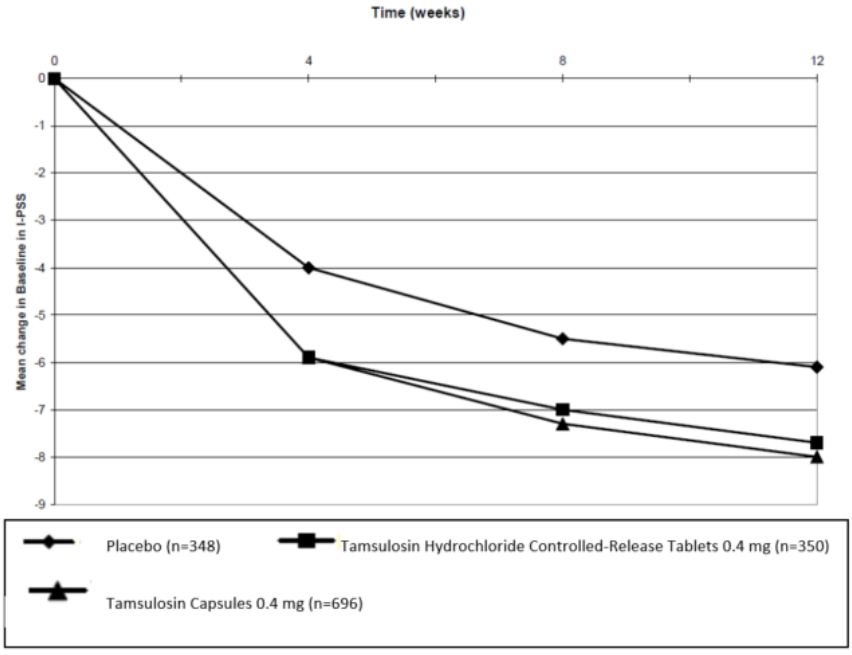


FIGURE 3: MEAN CHANGE FROM BASELINE IN TOTAL I-PSS OVER TIME IN THE PLACEBO- AND ACTIVE-CONTROLLED STUDY



In both studies, tamsulosin hydrochloride controlled-release tablets 0.4 mg had a fast onset of action with decrease in I-PSS at 2 to 4 weeks. As evident from Table 7 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.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single dose, crossover comparative bioavailability study of APO-TAMSULOSIN HCL 0.4 mg Controlled-Release tablets (Apotex Inc.) and FLOMAX® 0.4 mg CR tablets (Boehringer Ingelheim (Canada), Ltd.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 30 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOVAILABILITY DATA

Tamsulosin (1 x 0.4 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	96.47 110.62 (49.54)	94.41 110.26 (56.07)	102.2	91.9 - 113.6
AUC_I[5] (ng·h/mL)	103.30 119.18 (47.34)	102.18 124.84 (58.56)	101.1	88.9 – 114.9
C_{max} (ng/mL)	5.27 5.59 (33.15)	4.79 5.06 (35.07)	110.2	99.4 - 122.1
T_{max}[3] (h)	5.00 (2.00 - 18.00)	4.00 (2.00 – 9.00)		
T_{half} [4,5] (h)	12.97 (27.86)	14.60 (45.38)		
[1] APO-TAMSULOSIN HCL (tamsulosin hydrochloride) Controlled -Release tablets, 0.4 mg (Apotex Inc.)				

Tamsulosin (1 x 0.4 mg) Geometric Mean Arithmetic Mean (CV%)
[2] FLOMAX® (tamsulosin hydrochloride) CR tablets, 0.4 mg (Boehringer Ingelheim (Canada), Ltd.) [3] Expressed as the median (range) only [4]Expressed as the arithmetic mean (CV %) only [5]29 subjects for Test and 28 subjects for Reference product were included in calculations.

A randomized, two-way, single dose, crossover comparative bioavailability study of APO-TAMSULOSIN HCL 0.4 mg Controlled-Release tablets (Apotex Inc.) and FLOMAX® 0.4 mg CR tablets (Boehringer Ingelheim (Canada), Ltd.) was conducted in healthy, adult, male subjects under fed conditions. Comparative bioavailability data from the 18 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOVAILABILITY DATA

Tamsulosin (1 x 0.4 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	140.12 148.67 (36.32)	145.74 158.19 (42.33)	96.1	83.9 – 110.2
AUC_I (ng·h/mL)	147.47 156.06 (35.28)	152.51 164.81 (41.09)	96.7	84.9 – 110.1
C_{max} (ng/mL)	7.27 7.55 (28.45)	8.58 9.20 (40.60)	84.7	75.4 – 95.2
T_{max}[3] (h)	5.00 (4.00 – 12.00)	7.00 (3.00 – 10.00)		
T_{half}[4] (h)	13.41 (35.23)	13.28 (33.48)		

Tamsulosin (1 x 0.4 mg) Geometric Mean Arithmetic Mean (CV%)
[1] APO -TAMSULOSIN HCL (tamsulosin hydrochloride) Controlled -Release tablets, 0.4 mg (Apotex Inc.) [2] FLOMAX® (tamsulosin hydrochloride) CR tablets, 0.4 mg (Boehringer Ingelheim (Canada), Ltd.) [3] Expressed as the median (range) only [4]Expressed as the arithmetic mean (CV %) only

A randomized, two-way, multiple dose, single dose, crossover comparative bioavailability study of APO-TAMSULOSIN HCL 0.4 mg Controlled-Release tablets (Apotex Inc.) and FLOMAX® 0.4 mg CR tablets (Boehringer Ingelheim (Canada), Ltd.) was conducted in healthy, adult, male subjects under steady State fasting conditions. Comparative bioavailability data from the 33 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOVAILABILITY DATA

Tamsulosin (7 x 0.4 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{tau} (ng·h/mL)	101.81 109.92 (40.92)	110.65 128.33 (61.24)	92.0	83.2 – 101.8
C_{max} (ng/mL)	7.99 8.38 (32.14)	8.11 9.02 (51.10)	98.5	90.3- 107.4
C_{min} (ng·h/mL)	2.05 2.42 (60.63)	2.47 3.14 (75.49)	82.8	70.9 – 96.7
T_{max}[3] (h)	4.00 (2.00 – 6.00)	4.00 (3.00 – 7.00)		
Fluc[4] (%)	140.78 (29.64)	123.83 (37.90)		
[1] APO -TAMSULOSIN HCL (tamsulosin hydrochloride) Controlled -Release tablets, 0.4 mg				

Tamsulosin (7 x 0.4 mg) Geometric Mean Arithmetic Mean (CV%)
(Apotex Inc.) [2] FLOMAX® (tamsulosin hydrochloride) CR tablets, 0.4 mg (Boehringer Ingelheim (Canada), Ltd.) [3] Expressed as the median (range) only [4]Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

See 10 CLINICAL PHARMACOLOGY section.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity:

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Flomax® CR (Tamsulosin Hydrochloride Controlled Release Tablets, 0.4 mg), submission control 277510, Product Monograph, Boehringer Ingelheim (Canada) Ltd. (DEC 19, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-TAMSULOSIN CR

Tamsulosin Hydrochloride Controlled-Release Tablets

Read this carefully before you start taking **APO-TAMSULOSIN CR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-TAMSULOSIN CR.**

What is APO-TAMSULOSIN CR used for?

- APO-TAMSULOSIN CR is used to treat the urinary tract symptoms associated with a medical condition called benign prostatic hyperplasia (BPH).

How does APO-TAMSULOSIN CR work?

APO-TAMSULOSIN CR works by relaxing muscles in the prostate and bladder neck at the site of blockage, resulting in improved urine flow, and reduced BPH symptoms.

BPH is an enlargement of the prostate gland. BPH is the most common cause of lower urinary tract symptoms (LUTS) in older males.

After age 50, most men develop enlarged prostates. The prostate is located below the bladder. As the prostate enlarges, it may slowly restrict the flow of urine. This can lead to symptoms such as:

- frequent sleep interruption caused by a need to urinate;
- having a weak urinary stream;
- a sensation of not emptying your bladder completely after you finish urinating;
- pushing or straining to begin urination;
- stopping and starting again several times when urinating;
- urinating again less than 2 hours after you finish urinating;
- finding it difficult to delay urination.

What are the ingredients in APO-TAMSULOSIN CR?

Medicinal ingredient: Tamsulosin hydrochloride

Non-medicinal ingredients: Citric acid, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2208 and 2910, magnesium stearate, polyethylene glycol, sodium alginate, and yellow ferric oxide.

APO-TAMSULOSIN CR comes in the following dosage forms:

Controlled-release tablets containing 0.4 mg tamsulosin hydrochloride.

Do not use APO-TAMSULOSIN CR if:

- you are allergic to tamsulosin or any of the other ingredients in APO-TAMSULOSIN CR or any part of the container.
- you are taking ketoconazole (an antifungal used to treat fungal skin infections).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-TAMSULOSIN CR. Talk about any health conditions or problems you may have, including if you:

- have severe liver problems;
- have fainted due to low blood pressure when going to sit or stand up;
- are allergic to medicines used to treat infections called "sulfonamides" or "sulfa drugs";
- have kidney problems;
- have previously taken APO-TAMSULOSIN CR and became unwell;
- are going to have eye surgery for cataracts (cloudiness of the lens of the eye) and/or glaucoma (high pressure inside the eye).

Other warnings you should know about:

- **Driving and Using Machines:**
  - APO-TAMSULOSIN CR may cause dizziness. Do NOT drive, use machines or perform hazardous tasks for 12 hours after taking APO-TAMSULOSIN CR, or until you know how it affects you.

- **Fainting:**
  - APO-TAMSULOSIN CR may cause you to faint. If you feel dizzy or weak, you should sit or lie down until you feel better.

- **Check-ups and testing:**
  - **You must see your healthcare professional regularly**. While taking APO-TAMSULOSIN CR, you must have regular checkups. Follow your healthcare professional's advice about when to have these checkups.

- **APO-TAMSULOSIN CR should not be used in women or children.**

- **Surgery:**
  - Tell the healthcare professional you are seeing for the surgery that you are taking this medicine.

- If you are going to have eye surgery because of cataracts (cloudiness of the lens of the eye) or glaucoma (high pressure inside the eye) and are already taking or have previously taken APO-TAMSULOSIN CR, tell your healthcare professional.
  - The pupil may dilate poorly, and the iris (the coloured circular part of the eye) may become floppy during the surgery. This condition is known as "Intraoperative Floppy Iris Syndrome (IFIS)".
  - This condition has been seen in patients using APO-TAMSULOSIN CR and have surgery for cataracts or glaucoma.
- Ask your healthcare professional if you need to stop taking this medicine for a period of time before your surgery.

- **Fertility – information for men:**
  - Taking APO-TAMSULOSIN CR may lead to a condition called "ejaculation disorder." This is when you have an abnormal ejaculation where the semen does not leave the body through the urethra but instead goes into your bladder (retrograde ejaculation).
    - It is also possible for less semen or no semen to be released at all (ejaculation failure).
    - Talk to your healthcare professional if you experience this condition.
  - You may also experience a condition called "Priapism." This is when you experience a painful and prolonged unwanted erection of the penis (that will not go away through sexual intercourse or masturbation).
    - If not addressed, this condition can lead to the permanent loss of the ability to have an erection (erectile dysfunction or impotence).
    - If you experience this condition, stop taking the drug and get immediate medical help.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with APO-TAMSULOSIN CR:

- medicines used to lower blood pressure
  - Taking APO-TAMSULOSIN CR with other medicines from the same class (alpha$_1$-adrenoceptor blockers like doxazosin, prazosin, and terazosin) may cause an unwanted decrease in blood pressure.
- medicines used to treat erectile dysfunction called "PDE5 inhibitors" like sildenafil and tadalafil.
- ketoconazole (used to treat fungal infections on the skin).
- cimetidine (used to treat heartburn and stomach ulcers).
- warfarin (used to prevent blood clots).

How to take APO-TAMSULOSIN CR:

- Take APO-TAMSULOSIN CR exactly as your healthcare professional has told you.
- Swallow APO-TAMSULOSIN CR tablets whole Do NOT crush or chew APO-TAMSULOSIN CR tablets.
- This medicine has been prescribed specifically for you. Do NOT give your APO-TAMSULOSIN CR to anyone else. It may harm them even if their symptoms seem to be similar to yours.
- If you stop your medicine for several days or more, talk to your healthcare professional before taking APO-TAMSULOSIN CR again.
- APO-TAMSULOSIN CR can be taken with or without food.

Usual dose:

You should take one tablet (0.4 mg) once a day at the same time each day.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-TAMSULOSIN CR, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of APO-TAMSULOSIN CR at your usual time, you may take the missed dose later in the same day.
- If you miss a dose for a day, skip the missed dose. Take your next dose at the usual time.
- Do NOT take two doses to make up for a missed dose.

What are possible side effects from using APO-TAMSULOSIN CR?

These are not all the possible side effects you may have when taking APO-TAMSULOSIN CR. If you experience any side effects not listed here, tell your healthcare professional.

- abnormal ejaculation
- headache
- runny or blocked nose (rhinitis)
- diarrhea
- vomiting
- feeling sick (nausea)
- constipation
- weakness (asthenia)
- blurred or impaired vision
- nose bleeds (epistaxis)
- serious skin rashes (erythema multiform, dermatitis exfoliative)
- dry mouth
- skin sensitivity to light

- chest discomfort

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediately medical help**
	Only if severe	**In all cases**	
COMMON			
Dizziness: particularly when getting up from a seated or lying position		✓	
UNCOMMON			
Palpitations (feeling of rapid beating of the heart that may be more forceful)		✓	
Urticaria (Rashes, itching and hives)			✓
Orthostatic Hypotension (Reduced blood pressure): when getting up quickly from a seated or lying position, sometimes associated with dizziness		✓	
RARE			
Fainting			✓
Allergic Reaction (Hypersensitivity): Sudden local swelling of the soft tissues of the body (e.g., the throat or tongue), difficulty breathing and/or itching and rash (angioedema)			✓
VERY RARE			
Priapism (painful prolonged unwanted erection)			✓
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about APO-TAMSULOSIN CR:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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