

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **TAMSULOSIN CR**

Tamsulosin Hydrochloride Controlled-Release Tablets

Controlled-Release Tablets, 0.4 mg, Oral

Selective Antagonist of Alpha<sub>1a/1d</sub> Adrenoreceptor subtypes In the prostate and bladder

Sivem Pharmaceuticals ULC  
4705 Dobrin Street  
Saint-Laurent, Quebec, Canada  
H4R 2P7  
www.sivem.ca

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**RECENT MAJOR LABEL CHANGES**

|   |         |
|---|---------|
| <a href="#">1 INDICATIONS, 1.1 Pediatrics</a> | 10/2024 |
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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

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):**

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 [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 2-16 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 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**

- TAMSULOSIN CR is contraindicated in patients known to have hypersensitivity including drug induced angioedema to tamsulosin or any component of the TAMSULOSIN CR controlled release formulation. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#) section of the Product Monograph.
- 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**

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

TAMSULOSIN CR should be taken at the same time each day with or without food. TAMSULOSIN CR tablets must be swallowed whole, as crushing or chewing will interfere with the controlled release of the active ingredient.

Taking 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 CR tablets. These tablets are specially formulated to control the delivery of tamsulosin HCl to the blood stream.

#### 4.5 Missed Dose

If a dose of 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 tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosage.

Should overdosage of 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 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 30X 0.4 mg tamsulosin hydrochloride sustained release 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 0.4 mg of tamsulosin HCl | black iron oxide (E172), butylhydroxytoluene, carmine (E120), colloidal anhydrous silica, hydroxypropylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, quinoline yellow (E104), talc, titanium dioxide |

TAMSULOSIN CR are brown, round, biconvex tablets with debossing “0.4” on one side and “SZ” on the other side.

TAMSULOSIN CR (tamsulosin hydrochloride) 0.4 mg is supplied in HDPE bottles of 100 and 500 tablets.

## 7 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 controlled-release tablets, 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 CR should be cautioned to avoid situations where injury could result should syncope occur (see [8 ADVERSE REACTIONS](#)).**

### General

TAMSULOSIN CR (tamsulosin hydrochloride) 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 CR, requiring caution in people who must drive, operate

machinery, or perform hazardous tasks.

### **Drug-Drug Interactions**

- Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6. TAMSULOSIN CR should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). 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.
- TAMSULOSIN CR should be used with caution in combination with cimetidine.
- TAMSULOSIN CR should not be used in combination with other alpha adrenergic blocking agents.
- Caution is advised when alpha adrenergic blocking agents including tamsulosin hydrochloride 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 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. 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, the 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.

### **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 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 CR.

### **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 CR 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 CR 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 sustained-release capsules has been rarely reported. If a patient reports a serious or life-threatening sulfa allergy, caution is warranted when administering TAMSULOSIN CR.

## **7.3 Special Populations**

### **7.3.1 Pregnant Women**

TAMSULOSIN CR 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.

### **7.3.2 Breast-feeding**

TAMSULOSIN CR is not indicated for use in women.

### **7.3.3 Pediatrics**

TAMSULOSIN CR 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 ( $\geq 5\%$ ) were urinary tract infection, vomiting, nasopharyngitis, influenza, headache, and abdominal pain.

### **7.3.4 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 sustained-release capsules indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. However, tamsulosin hydrochloride sustained-release 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

### 8.3 Adverse Reaction Overview

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

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

### 8.4 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 controlled-release tablets 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 sustained-release capsules 0.4 mg and 568 with placebo. The results suggest that tamsulosin hydrochloride controlled-release tablets 0.4 mg and tamsulosin hydrochloride sustained-release 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 sustained-release 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  $\geq$  2% Of Patients Receiving Either Tamsulosin or Placebo During The 3 Month Placebo And Active-Controlled Study.**

| <b>SOC/Preferred term</b>                               | <b>Placebo<br/>N=356</b> | <b>Tamsulosin<br/>Hydrochloride<br/>Controlled Release<br/>Tablets 0.4 mg<br/><br/>N=360</b> | <b>Tamsulosin Capsules<br/>0.4 mg<br/><br/>N=709</b> |
|---|--------------------------|--|--|
| Any TEAE  | 71<br>(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<br>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<br>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<br>breast disorders             | 2 (0.6%)                 | 12 (3.3%)  | 28 (3.9%)  |
| Respiratory, thoracic and<br>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<br>N=356 | Tamsulosin Hydrochloride<br>Controlled Release Tablets<br>0.4mg<br>N=360 | Tamsulosin Capsules<br>0.4mg<br>N=709 |
|---|------------------|--|---------------------------------------|
| <b>Non-cardiovascular class effects</b> |                  |  |                                       |
| 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<br>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%)                             |
| <b>Cardiovascular class effects</b>     |                  |  |                                       |
| 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%)                              |

| <b>SOC/Preferred term</b>                   | <b>Placebo<br/>N=356</b> | <b>Tamsulosin Hydrochloride<br/>Controlled Release Tablets<br/>0.4mg<br/>N=360</b> | <b>Tamsulosin Capsules<br/>0.4mg<br/>N=709</b> |
|---|--------------------------|--|--|
| 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<br>collapse         | 0 (0.0%)                 | 0 (0.0%)   | 0 (0.0%)                                       |
| Depressed level of/loss of<br>consciousness | 0 (0.0%)                 | 1 (0.3%)   | 1 (0.1%)                                       |
| <b>SUB-TOTAL</b>                            | <b>8 (2.2%)</b>          | <b>9 (2.5%)</b>  | <b>23 (3.2%)</b>                               |
| <b>TOTAL</b>                                | <b>13 (3.7%)</b>         | <b>25 (6.9%)</b>   | <b>55 (7.8%)</b>                               |

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 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 (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 sustained-release capsules. As with tamsulosin hydrochloride sustained-release capsules, caution should be exercised with concomitant

administration of TAMSULOSIN CR and other alpha-adrenergic blocking agents.

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

### 9.3 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 hydrochloride sustained-release 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 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 hydrochloride sustained-release 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 is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin hydrochloride should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). TAMSULOSIN CR 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 have not been evaluated.

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

**Nifedipine, Atenolol, Enalapril:** No dosage adjustments are necessary when TAMSULOSIN CR is administered concomitantly with nifedipine, atenolol, or enalapril. In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of nifedipine, atenolol or enalapril for at least three months, tamsulosin hydrochloride sustained release 0.4 mg capsules for seven days followed by tamsulosin hydrochloride sustained

release 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 CR.

**Digoxin and Theophylline:** No dosage adjustments are necessary when TAMSULOSIN CR 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 sustained release capsules 0.4 mg/day for two days, followed by tamsulosin hydrochloride sustained release 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 CR is administered concomitantly with furosemide. The pharmacokinetic and pharmacodynamic interaction between tamsulosin hydrochloride sustained release 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 sustained release 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 tablet 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 sustained release 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. Therefore, TAMSULOSIN CR 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 are co-administered with PDE5 inhibitors.

### **Other Alpha-Adrenergic Blocking Agents**

The pharmacokinetic and pharmacodynamic interactions between tamsulosin hydrochloride and other alpha adrenergic blocking agents have not been determined; however, interactions between tamsulosin hydrochloride 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 <sup>1</sup>    | 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 sustained-release 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 CR should be used with caution in combination with cimetidine.  |
| Ketoconazole                 | CT <sup>2</sup>    | Coadministration of ketoconazole increased the C <sub>max</sub> and AUC from time zero to infinity (AUC <sub>∞</sub> ) of tamsulosin by 2.2- and 2.8-fold, respectively.  | TAMSULOSIN CR should not be given in combination with strong inhibitors of CYP3A4.   |
| Paroxetine                   | CT <sup>2</sup>    | Coadministration of paroxetine increased the C <sub>max</sub> and AUC <sub>∞</sub> of tamsulosin by factors of approximately 1.3 and 1.6, respectively.   | Increases in C <sub>max</sub> and AUC of tamsulosin hydrochloride controlled-release tablets are not considered clinically relevant. |
| α 1-adrenoceptor antagonists | T <sup>3, 4</sup>  | Concurrent administration of other α 1-adrenoceptor antagonists could lead to hypotensive effects.  | TAMSULOSIN CR should not be used in combination with other alpha adrenergic blocking agents.   |

| [Proper/Common name]  | Source of Evidence | Effect   | Clinical comment  |
|---|--------------------|--|---|
| Digoxin or Theophylline                                       | CT <sup>3, 5</sup> | Concurrent administration of digoxin with tamsulosin did not produce any change in the pharmacokinetics of digoxin or theophylline.  | No adjustment in TAMSULOSIN CR 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 are co-administered with PDE5 inhibitors.                         |
| Antihypertensives (e.g., nifedipine, enalapril, and atenolol) | CT <sup>6</sup>    | Tamsulosin hydrochloride did not interfere with or potentiate the antihypertensive action of nifedipine, enalapril, or atenolol.<br><br>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 <sup>7</sup>     | Erythromycin is a moderate inhibitor of CYP3A.   | TAMSULOSIN CR should be used with caution in combination with moderate inhibitors of CYP3A4.  |

| [Proper/Common name] | Source of Evidence | Effect  | Clinical comment  |
|----------------------|--------------------|---|---|
| Furosemide           | CT <sup>8</sup>    | The pharmacokinetic and pharmacodynamic interaction between tamsulosin hydrochloride sustained-release 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 sustained-release capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin C <sub>max</sub> and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin hydrochloride controlled-release tablets dosage. | No dosage adjustments are necessary when TAMSULOSIN CR 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

### 10.3 Mechanism of Action

Tamsulosin hydrochloride controlled-release tablets is an alpha<sub>1</sub> 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<sub>1A</sub> and alpha<sub>1D</sub> receptors over the alpha<sub>1B</sub> AR subtype. These three AR subtypes have a distinct distribution pattern in human tissue. Whereas approximately 70% of the alpha<sub>1</sub>-receptors in human prostate are of the alpha<sub>1A</sub> subtype, the human bladder contains predominantly the alpha<sub>1D</sub> subtype while blood vessels express predominantly alpha<sub>1B</sub> 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 CR is not intended for use as an antihypertensive drug.

#### 10.4 Pharmacodynamics

Tamsulosin hydrochloride controlled release tablets are 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.

#### 10.5 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 - 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. Under fasted conditions the absolute bioavailability of tamsulosin from tamsulosin hydrochloride controlled-release tablets was estimated to be 57%.

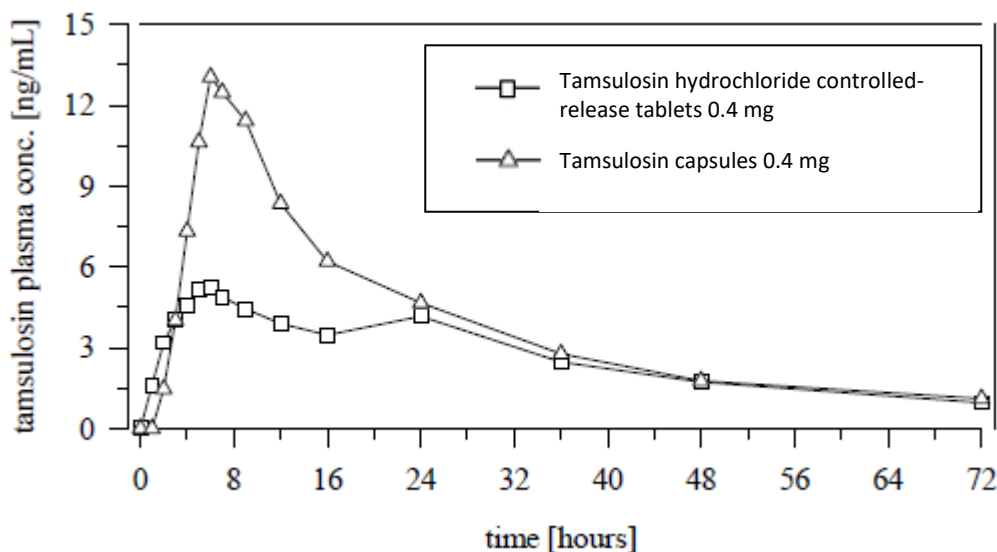
A study conducted at steady state with 0.4 mg tamsulosin hydrochloride controlled-release tablets demonstrated that the plasma concentration-time profile in the fed state was bioequivalent to the fasted state, indicating the absence of a food effect, by a low fat meal (Table 5). After a single oral dose 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 tablet 0.4mg (Fed) (n=24) | Tamsulosin hydrochloride controlled release tablet 0.4mg (Fasted) (n=24) |
|--------------------------------|---|--|
| AUC <sub>0-inf</sub> (ng.h/ml) | 291.1   | 278.7  |
| C <sub>max</sub> (ng/ml)       | 11.1  | 10.7   |
| C <sub>24</sub> (ng/ml)        | 4.8   | 4.6  |
| T <sub>max</sub> (h)           | 4.16  | 4.75   |
| T <sub>1/2</sub> (h)           | 14.6  | 15.6   |

The 0.4 mg tamsulosin hydrochloride controlled-release tablet is not bioequivalent to the 0.4 mg tamsulosin hydrochloride sustained-release capsule, as the test/reference ratio for C<sub>max</sub> 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<sub>max</sub> with tamsulosin hydrochloride controlled-release tablets compared with tamsulosin hydrochloride sustained-release 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 hydrochloride sustained-release 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 controlled release tablets 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 sustained release capsules indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. However, tamsulosin hydrochloride sustained release 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:** Tamsulosin hydrochloride controlled release tablets 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 – 30°C).

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

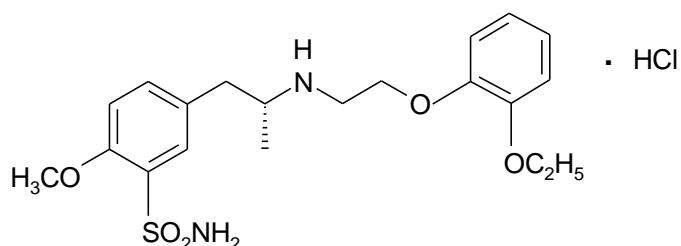
#### Drug Substance

Proper name: Tamsulosin hydrochloride

Chemical name: (-)-(R)-5-[2-[[2-o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide monohydrochloride.

Molecular formula and molecular mass:  $C_{20}H_{28}N_2O_5S \cdot HCl$ ; 444.98

Structural formula:



Physicochemical properties:

Tamsulosin HCl occurs as white crystals that melt with decomposition at approximately 230°C. It is sparingly soluble in water and in methanol, slightly soluble in glacial acetic acid and in ethanol, and practically insoluble in ether.

pH (7.5 mg/mL): 5.20

pKa: 8.37 (secondary amine) ; 10.23 (sulfonamide)

### 14 CLINICAL TRIALS

#### 14.3 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, placebo controlled | tamsulosin hydrochloride controlled release tablets 0.4 mg oral,<br>Placebo, oral<br>12-weeks   | tamsulosin hydrochloride controlled release tablets 0.4mg (203)<br>Placebo (211)                              | ≥ 45             | males |
| 617-CL-307 | Double-blind, randomized, placebo controlled | tamsulosin hydrochloride controlled release tablets 0.4 mg oral,<br>Tamsulosin capsules 0.4 mg, oral, 12-weeks<br>Placebo, oral<br>12 weeks | tamsulosin hydrochloride controlled release tablets 0.4mg (354)<br>Tamsulosin capsules (700)<br>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 sustained release 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.

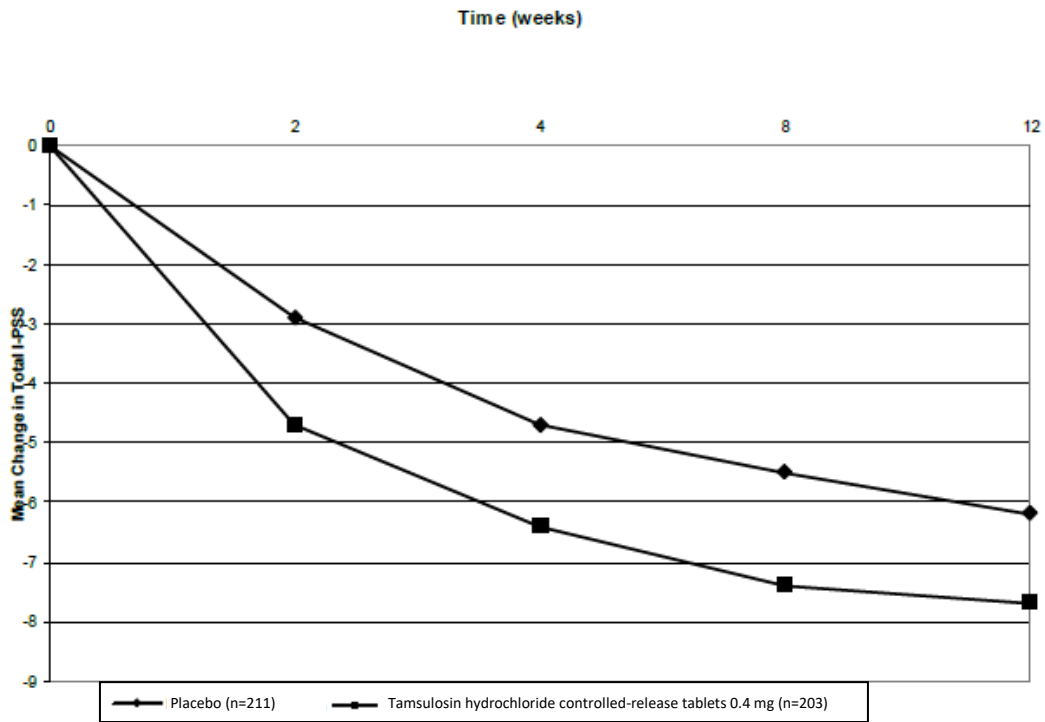
The primary efficacy parameter for both studies was the change from baseline to endpoint in Total I-PSS for the full analysis set (FAS). The I-PSS consists of questions that assess the severity of both irritative and obstructive symptoms, with possible scores ranging from 0 to 35. The secondary efficacy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

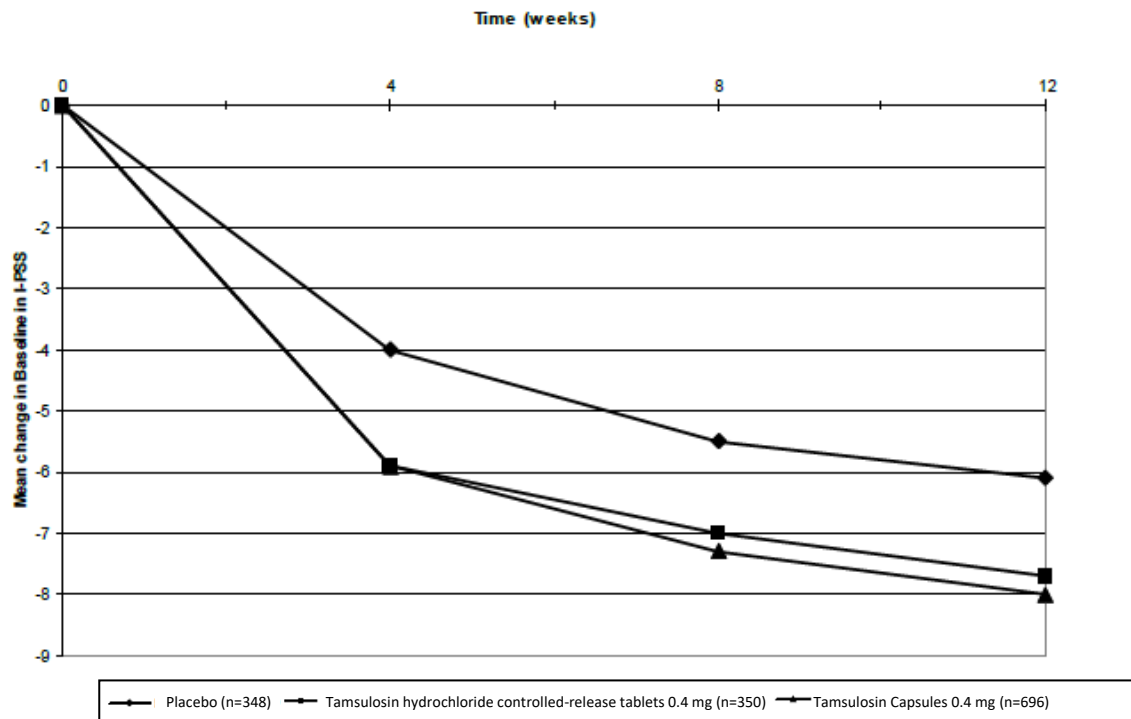
| Study #    | Treatment Arm  | No. Baseline/Endpoint | Baseline Mean (SD) | Endpoint Mean (SD) | Change at Endpoint Mean (SD) [%] | Difference vs. Placebo Mean (95% CI) | P-value vs. Placebo |
|------------|--|-----------------------|--------------------|--------------------|----------------------------------|--------------------------------------|-------------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

<sup>a</sup> 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 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 sustained release 0.4 mg capsules confirming the recommendation of once daily dosing of 0.4 mg.

#### 14.2 Comparative Bioavailability Studies

A comparative, single dose (0.4 mg dose as 1 x 0.4 mg), blinded, randomized, 2-way crossover bioequivalence study of TAMSULOSIN CR (tamsulosin hydrochloride controlled-release tablets) vs Flomax CR<sup>®</sup> (tamsulosin hydrochloride controlled-release tablets, Boehringer Ingelheim, Canada), was conducted on a total of 46 healthy male volunteers, aged 18-55 years, under fasting conditions.

| Tamsulosin<br>(1 x 0.4 mg)<br>Geometric Mean<br>Arithmetic Mean (CV %) |                               |                                |                               |                            |
|--|-------------------------------|--------------------------------|-------------------------------|----------------------------|
| Parameter  | Test <sup>1</sup>             | Reference product <sup>2</sup> | % Ratio of<br>Geometric Means | 90% Confidence<br>Interval |
| AUC <sub>T</sub><br>(pg·h/mL)  | 85230.80<br>100232.36 (59.36) | 95234.39<br>110756.98 (53.90)  | 89.5 %                        | 80.2 % to 99.9 %           |
| AUC <sub>I</sub><br>(pg·h/mL)  | 96997.08<br>117398.13 (62.64) | 107274.69<br>130448.45 (66.73) | 90.4 %                        | 79.1 % to 103.4 %          |
| C <sub>max</sub><br>(pg/mL)  | 4928.53<br>5423.85 (48.23)    | 5011.89<br>5384.21 (41.07)     | 98.3 %                        | 90.3 % to 107.1 %          |
| T <sub>max</sub> <sup>3</sup><br>(h)                                   | 4.50 (2.00 - 24.00)           | 4.50 (3.00 - 24.00)            |                               |                            |
| T <sub>½</sub> <sup>4</sup><br>(h)                                     | 14.15 (44.81)                 | 14.21 (41.91)                  |                               |                            |

<sup>1</sup> TAMSULOSIN CR (tamsulosin hydrochloride) controlled-release tablets 0.4 mg (Sivem Pharmaceuticals ULC)

<sup>2</sup> Flomax<sup>®</sup> CR (tamsulosin hydrochloride) controlled-release tablets 0.4 mg ((Boehringer Ingelheim (Canada) Ltd.) were purchased in Canada.

<sup>3</sup> Expressed as the median (range) only

<sup>4</sup> Expressed as the arithmetic mean (CV%) only

A comparative, single dose (0.4 mg dose as 1 x 0.4 mg), blinded, randomized, 2-way crossover bioequivalence study of TAMSULOSIN CR (tamsulosin hydrochloride controlled-release tablets) vs Flomax CR<sup>®</sup> (tamsulosin hydrochloride controlled-release tablets, Boehringer Ingelheim,

Canada), was conducted on a total of 25 healthy male volunteers, aged 18-55 years, under fed conditions (high-fat high-calorie).

| Tamsulosin Hydrochloride<br>(1 x 0.4 mg)<br>Geometric Mean<br>Arithmetic Mean (CV %) |                                |                                |                            |                         |
|--|--------------------------------|--------------------------------|----------------------------|-------------------------|
| Parameter  | Test <sup>1</sup>              | Reference <sup>2</sup>         | % Ratio of Geometric Means | 90% Confidence Interval |
| AUC <sub>T</sub><br>(pg·h/mL)  | 146393.08<br>155162.63 (30.92) | 153622.89<br>161690.74 (32.68) | 95.3%                      | 88.6% to 102.5%         |
| AUC <sub>I</sub><br>(pg·h/mL)  | 162224.99<br>171414.06 (30.65) | 165344.01<br>174817.18 (34.06) | 98.1%                      | 91.2% to 105.5%         |
| C <sub>max</sub><br>(pg/mL)  | 9406.47<br>9830.45 (28.44)     | 8964.18<br>9380.37 (33.62)     | 104.9%                     | 94.3% to 116.8%         |
| T <sub>max</sub> <sup>3</sup><br>(h)   | 5.00 (3.00 - 12.10)            | 8.00 (2.00 - 24.00)            |                            |                         |
| T <sub>½</sub> <sup>4</sup><br>(h)   | 13.25 (33.24)                  | 11.09 (25.42)                  |                            |                         |

<sup>1</sup>TAMSULOSIN CR (tamsulosin hydrochloride) controlled-release tablets 0.4 mg (Sivem Pharmaceuticals ULC)

<sup>2</sup>Flomax<sup>®</sup> CR (tamsulosin hydrochloride) controlled-release tablets 0.4 mg ((Boehringer Ingelheim (Canada) Ltd.) were purchased in Canada.

<sup>3</sup> Expressed as the median (range) only

<sup>4</sup> Expressed as the arithmetic mean (CV%) only

A comparative, multiple dose (0.4 mg dose as 1 x 0.4 mg daily during 7 consecutive days), blinded, randomized, 2-way crossover bioequivalence study of TAMSULOSIN CR (tamsulosin hydrochloride controlled-release tablets) vs Flomax CR<sup>®</sup> (tamsulosin hydrochloride controlled-release tablets, Boehringer Ingelheim (Canada) Ltd.), was conducted on a total of 40 healthy male volunteers, aged 18-55 years, under fasting conditions.

| Tamsulosin<br>(1 x 0.4 mg)               |                                |                                |                               |                            |
|--|--------------------------------|--------------------------------|-------------------------------|----------------------------|
| Geometric Mean<br>Arithmetic Mean (CV %) |                                |                                |                               |                            |
| Parameter                                | Test <sup>1</sup>              | Reference product <sup>2</sup> | % Ratio of<br>Geometric Means | 90% Confidence<br>Interval |
| AUC <sub>tau</sub><br>(pg·h/mL)          | 130636.93<br>148764.43 (62.75) | 124261.72<br>133863.34 (44.09) | 105.1 %                       | 95.5 % to 115.8 %          |
| C <sub>max</sub><br>(pg/mL)              | 9521.77<br>10479.85 (48.38)    | 9355.86<br>10016.58 (39.04)    | 101.8 %                       | 92.9 % to 111.6 %          |
| C <sub>min</sub><br>(pg/mL)              | 2769.59<br>3520.21 (88.41)     | 2523.18<br>2979.81 (65.08)     | 109.8 %                       | 94.06 % to 128.1 %         |
| T <sub>max</sub> <sup>3</sup><br>(h)     | 4.01 (2.00 - 7.50)             | 4.50 (2.00 - 8.00)             |                               |                            |
| FI<br>(%)                                | 125.38 (32.04)                 | 134.42 (32.08)                 |                               |                            |

<sup>1</sup>TAMSULOSIN CR (tamsulosin hydrochloride) controlled-release tablets 0.4 mg (Sivem Pharmaceuticals ULC.)

<sup>2</sup>Flomax<sup>®</sup> CR (tamsulosin hydrochloride) controlled-release tablets 0.4 mg ((Boehringer Ingelheim (Canada) Ltd.) were purchased in Canada.

<sup>3</sup>Expressed as the median (range) 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  $\geq 5.4$  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. <sup>Pr</sup> FLOMAX<sup>®</sup> CR, tamsulosin hydrochloride controlled-release tablets, 0.4 mg, submission control 277510, Product Monograph, Boehringer Ingelheim (Canada) Inc. DEC 19, 2023.

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

#### **Pr TAMSULOSIN CR**

#### **Tamsulosin Hydrochloride Controlled-Release Tablets**

Read this carefully before you start taking **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 **TAMSULOSIN CR**.

#### **What is TAMSULOSIN CR used for?**

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

#### **How does TAMSULOSIN CR work?**

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 TAMSULOSIN CR?**

Medicinal ingredient: Tamsulosin hydrochloride

Non-medicinal ingredients: Black iron oxide (E172), butylhydroxytoluene, carmine (E120), colloidal anhydrous silica, hydroxypropylcellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, quinoline yellow (E104), talc, titanium dioxide.



**TAMSULOSIN CR comes in the following dosage forms:**

Controlled-release tablets containing 0.4 mg tamsulosin hydrochloride.

**Do not use TAMSULOSIN CR if:**

- you are allergic to tamsulosin or any of the other ingredients in 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 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 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:**
  - TAMSULOSIN CR may cause dizziness. Do NOT drive, use machines or perform hazardous tasks for 12 hours after taking TAMSULOSIN CR, or until you know how it affects you.
- **Fainting:**
  - 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 TAMSULOSIN CR, you must have regular checkups. Follow your healthcare professional’s advice about when to have these checkups.
- **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 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 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 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 TAMSULOSIN CR:**

- medicines used to lower blood pressure
  - Taking TAMSULOSIN CR with other medicines from the same class (alpha<sub>1</sub>-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 TAMSULOSIN CR:**

- Take TAMSULOSIN CR exactly as your healthcare professional has told you.
- Swallow TAMSULOSIN CR tablets whole. Do NOT crush or chew TAMSULOSIN CR tablets.

- This medicine has been prescribed specifically for you. Do NOT give your 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 TAMSULOSIN CR again.
- 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 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 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 TAMSULOSIN CR?**

These are not all the possible side effects you may have when taking 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 immediate medical help |
|  | Only if severe                       | In all cases |   |
| <b>COMMON</b>  |                                      |              |   |
| <b>Dizziness:</b> particularly when getting up from a seated or lying position   |                                      | ✓            |   |
| <b>UNCOMMON</b>  |                                      |              |   |
| <b>Palpitations (feeling of rapid beating of the heart that may be more forceful)</b>  |                                      | ✓            |   |
| <b>Urticaria (Rashes, itching and hives)</b>   |                                      |              | ✓   |
| <b>Orthostatic Hypotension (Reduced blood pressure):</b> when getting up quickly from a seated or lying position, sometimes associated with dizziness  |                                      | ✓            |   |
| <b>RARE</b>  |                                      |              |   |
| <b>Fainting</b>  |                                      |              | ✓   |
| <b>Allergic Reaction (Hypersensitivity):</b> Sudden local swelling of the soft tissues of the body (e.g., the throat or tongue), difficulty breathing and/or itching and rash (angioedema)   |                                      |              | ✓   |
| <b>VERY RARE</b>   |                                      |              |   |
| <b>Priapism (painful prolonged unwanted erection)</b>  |                                      |              | ✓   |
| <b>Stevens-Johnson syndrome (SJS) (severe skin rash):</b> 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 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 [www.sivem.ca](http://www.sivem.ca), or by calling 1-855-788-3153.

This leaflet was prepared by Sivem Pharmaceuticals ULC.

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