PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **SANDOZ TAMSULOSIN**

Tamsulosin Hydrochloride Sustained-Release Capsules

Capsules, Sustained-Release, 0.4 mg, Oral

USP

Selective Antagonist of

$Alpha_{1A}$ Adrenoreceptor subtype

In the Prostate

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	05/2024

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Tamsulosin (tamsulosin hydrochloride sustained release capsules) is indicated for:

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

1.1 Pediatrics (<16 years of age)

Sandoz Tamsulosin 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 Sandoz Tamsulosin 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 and 0.8 mg once daily) to patients over the age of 65 years.

2 CONTRAINDICATIONS

- Sandoz Tamsulosin is contraindicated in patients known to have hypersensitivity including drug-induced angioedema to tamsulosin or any component of the Sandoz Tamsulosin sustained release formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Sandoz Tamsulosin 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

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

Depending on individual patient symptomatology and/or flow rates, the dose may be adjusted to 0.8 mg once daily. If tamsulosin administration is discontinued or interrupted for several days at either the 0.4 or 0.8 mg dose, therapy should be reinstituted, beginning with the 0.4 mg once daily dose.

4.4 Administration

Sandoz Tamsulosin should be administered approximately one-half hour following the same meal each day.

Taking Sandoz Tamsulosin 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, chew or open Sandoz Tamsulosin capsules. These capsules are specially formulated to control the delivery of tamsulosin HCl to the blood stream.

4.5 Missed Dose

If a dose of Sandoz Tamsulosin 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 Sandoz Tamsulosin 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 diarrhea 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 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 center.

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	Sustained-release capsules/0.4 mg/corresponding to 0.4 mg of tamsulosin HCl	Methacrylic acid-ethyl acrylate copolymer, microcrystalline cellulose, polyacrylate, polysorbate 80, purified water, sodium lauryl sulphate and talc Capsule shell contains: black iron oxide, gelatine, indigo carmine, red iron oxide, titanium dioxide and yellow iron oxide. Capsule imprinting ink contains TekPrint SW-9008 Blank Ink: black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac and strong ammonia solution. Opacode Black S-1-27794: Industrial methylated spirit 74 OP, Iron oxide black JPE, Isopropyl alcohol, N-butyl alcohol, Propylene glycol, Purified water, Shellac glaze – 47.5 % (22 % esterified) IN IMS 74 OP.

Sandoz Tamsulosin (tamsulosin hydrochloride) are coated modified release pellets, filled into hard gelatine capsules of size 2, with olive green cap and orange body. The capsules are imprinted axially on both sides with “0.4”.

Packaging

Sandoz Tamsulosin is available in HDPE bottles of 100 sustained-released capsules.

7 WARNINGS AND PRECAUTIONS

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

General

Sandoz Tamsulosin 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 coexist. 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 sustained-release capsules and the ability to drive vehicles or use machinery. However, patients should be advised that dizziness can occur with Sandoz Tamsulosin, requiring caution in people who must drive, operate machinery, or perform hazardous tasks.

Drug-Drug Interactions

- Tamsulosin is extensively metabolized, mainly by CYP3A and CYP2D6. Sandoz Tamsulosin should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). Sandoz Tamsulosin 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.
- Sandoz Tamsulosin should be used with caution in combination with cimetidine.
- Sandoz Tamsulosin should not be used in combination with other alpha adrenergic blocking agents.
- Caution is advised when alpha adrenergic blocking agents including Sandoz Tamsulosin 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 Sandoz Tamsulosin.

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 are known. Treatment with tamsulosin 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. Most reports to date were in patients taking tamsulosin when IFIS occurred, but in some cases, tamsulosin had been stopped prior to surgery. In most of these cases, tamsulosin 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 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 Sandoz Tamsulosin, 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 α_1-adrenoceptor antagonists, other symptoms can occur (dizziness and postural hypotension). In the two U.S. double-blind, placebo-controlled studies (Studies 1 and 2), orthostatic testing was conducted at each visit. Postural hypotension was reported in three patients (0.6%) receiving tamsulosin capsules.

In 2102 patients included in U.S., European, and Japanese placebo-controlled clinical studies, 0.3% of patients receiving tamsulosin capsules experienced postural hypotension, 10.2% experienced dizziness, and 0.7% experienced vertigo; patients receiving placebo experienced postural hypotension, dizziness, and vertigo at rates of 0.1%, 7.2%, and 0.4%, respectively.

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 Sandoz Tamsulosin.

Renal

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

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 Sandoz Tamsulosin 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: Sandoz Tamsulosin 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 capsules has been rarely reported. If a patient reports a serious or life-threatening sulfa allergy, caution is warranted when administering Sandoz Tamsulosin.

7.1 Special Populations

7.1.1 Pregnant Women

Sandoz Tamsulosin 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

Sandoz Tamsulosin is not indicated for use in women.

7.1.3 Pediatrics

Sandoz Tamsulosin 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. Cross-study comparisons of overall exposure (AUC) and half-life of tamsulosin capsules indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. However, tamsulosin 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 tamsulosin hydrochloride (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.

The incidence of treatment emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg tamsulosin were used. These studies evaluated safety in 1783 patients treated with tamsulosin and 798 patients administered placebo. The data suggest that tamsulosin is generally well tolerated at daily dose levels ranging from 0.1 to 0.8 mg. Adverse events seen were generally mild, transient, and self-limiting. Table 1 summarizes the treatment emergent adverse events occurring in 1% of patients receiving either tamsulosin or placebo during these six short-term, (U.S. and European) placebo-controlled trials.

No new types of AEs were apparent after long-term treatment with tamsulosin. Those AEs reported with the higher incidence by patients receiving tamsulosin compared to those receiving placebo in the short-term studies were reported with a similar pattern in the long-term studies.

Table 2: Treatment-Emergent Adverse Events occurring in 1% of Tamsulosin or Placebo Patients During Short-Term (U.S. and European) Placebo-Controlled Trials[1]

Body System / Adverse Event	**Tamsulosin (N=1783)**	**Placebo (N=798)**
Body As A Whole		
Headache	14.7%	15.5%
Infection	7.9%	6.8%
Pain	7.6%	7.3%
Asthenia	6.1%	5.0%
Back Pain	6.2%	4.5%
Abdominal Pain	3.4%	4.3%
Chest Pain	3.3%	3.1%
Accidental Injury	2.1%	3.0%
Flu Syndrome	2.1%	2.9%
Neck Pain	1.0%	1.1%
Fever	1.0%	1.0%
Chills	0.7%	1.0%
Malaise	0.4%	1.1%
Cardiovascular System		
Hypertension	0.9%	1.1%
Digestive System		
Diarrhea	4.4%	4.4%
Dyspepsia	3.8%	5.4%
Nausea	2.6%	2.9%
Constipation	1.3%	1.4%
Tooth Disorder	1.1%	0.9%
Metabolic And Nutritional Disorders		
Peripheral Edema	0.8%	1.0%

Body System / Adverse Event	Tamsulosin (N=1783)	Placebo (N=798)
Musculoskeletal System		
Arthralgia	3.0%	3.3%
Myalgia	1.7%	2.1%
Arthritis	1.1%	1.0%
Nervous System		
Dizziness	11.8%	8.9%
Somnolence	2.5%	1.5%
Insomnia	1.7%	0.6%
Hypertonia	1.1%	1.5%
Libido Decreased	1.2%	0.9%
Paresthesia	0.4%	1.1%
Respiratory System		
Rhinitis	11.6%	6.9%
Pharyngitis	4.3%	3.9%
Cough Increased	3.1%	2.4%
Sinusitis	2.1%	1.3%
Dyspnea	1.1%	1.1%
Lung Disorder	1.1%	0.9%
Skin And Appendages		
Rash	1.8%	1.8%
Pruritus	1.0%	1.0%
Sweating	1.1%	0.8%
Urogenital System		
Abnormal Ejaculation	8.7%	0.5%
Urinary Tract Infection	1.5%	0.4%
Dysuria	1.2%	1.3%
Impotence	1.2%	1.5%

[1] Adverse events from patients given 0.1-0.8 mg tamsulosin daily were pooled.

Adverse reactions occuring in < 1% of the tamsulosin and placebo patient population include amblyopia, with a frequency of 0.6% and 0.2%, respectively.

Tamsulosin has not been associated with any clinically significant changes in the urinalysis or the routine biochemical and hematologic tests.

Table 3 shows the treatment emergent adverse events from which ≥ 0.5% of the patients administered tamsulosin (N=1783) placebo (N=798) discontinued U.S. and European short-term, placebo-controlled clinical studies. The most frequent adverse events resulting in discontinuation of tamsulosin treatment were dizziness, asthenia, abnormal ejaculation, and chest pain.

Table 3: Description of Discontinuation Occurring in ≥ 0.5% of Tamsulosin or Placebo Patients in U.S. and European Short-Term Placebo-Controlled Clinical Studies[1]

Body System/ Adverse Event	Tamsulosin (N=1783)	Placebo (N =798)
Body As a Whole		
Asthenia	0.7%	0.6%
Headache	0.4%	0.6%
Chest Pain	0.5%	0.3%
Nervous System		
Dizziness	1.4%	0.9%
Urogenital System		
Abnormal Ejaculation[2]	0.6%	0%

[1] Adverse events from patients given 0.1-0.8 mg tamsulosin daily were pooled.

[2] Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation and ejaculation decrease. Abnormal ejaculation was dose related in U.S. studies 8.4% in 0.4 mg group 18.1% in 0.8 mg group. Withdrawal from these clinical studies of tamsulosin because of abnormal ejaculation was also dose dependent 1.6% in the 0.8 mg group, and no patients in the 0.4 mg or placebo groups.

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 (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

The pharmacokinetic and pharmacodynamic interactions between tamsulosin and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and caution should be exercised with concomitant administration of tamsulosin capsules and alpha-adrenergic blocking agents.

No clinically significant drug-drug interactions were observed when tamsulosin 0.4 mg or 0.8 mg was 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 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 is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). Tamsulosin should be given with caution in combination with moderate inhibitors of CYP3A4.

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

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

Nifedipine, Atenolol, Enalapril: No dosage adjustments are necessary when tamsulosin 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 0.4 mg capsules for seven days followed by tamsulosin 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 Sandoz Tamsulosin.

Digoxin and Theophylline: No dosage adjustments are necessary when Sandoz Tamsulosin is administered concomitantly with digoxin or theophylline. In two studies in healthy volunteers (n=10 per study; age range 19-39 years), receiving tamsulosin 0.4 mg/day for two days, followed by tamsulosin 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 Sandoz Tamsulosin is administered concomitantly with furosemide. The pharmacokinetic and pharmacodynamic interaction between tamsulosin 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 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 Sandoz Tamsulosin 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 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, Sandoz Tamsulosin 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 Sandoz Tamsulosin are co-administered with PDE5 inhibitors.

Other Alpha-Adrenergic Blocking Agents

The pharmacokinetic and pharmacodynamic interactions between Sandoz Tamsulosin and other alpha-adrenergic blocking agents have not been determined; however, interactions between Sandoz 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 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.	Sandoz Tamsulosin 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.	Sandoz Tamsulosin should not be given in combination with strong inhibitors of CYP3A4.
Paroxetine	CT[2]	Coadministration of paroxetine increased the C_{max} and AUC $_{\infty}$ of tamsulosin by factors of approximately 1.3 and 1.6, respectively.	Increases in C_{max} and AUC of tamsulosin 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.	Sandoz Tamsulosin 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 Sandoz Tamsulosin 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	Caution is advised when alpha

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
		can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.	adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors.
Antihypertensives (e.g., nifedipine, enalapril, and atenolol)	CT[6]	Tamsulosin 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 was given.
Erythromycin	T[7]	Erythromycin is a moderate inhibitor of CYP3A.	Sandoz Tamsulosin should be used with caution in combination with moderate inhibitors of CYP3A4.
Furosemide	CT[8]	The pharmacokinetic and pharmacodynamic interaction between tamsulosin 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 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 Sandoz Tamsulosin dosage.	No dosage adjustments are necessary when Sandoz Tamsulosin is administered concomitantly with furosemide.

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sandoz Tamsulosin (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 alpha$_1$ receptors in the human prostate. At least three discrete alpha$_1$ adrenoreceptor subtypes have been identified: alpha$_{1A}$, alpha$_{1B}$ and alpha$_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the alpha$_1$-receptor in human prostate are of the alpha$_{1A}$ 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.

Sandoz Tamsulosin (tamsulosin hydrochloride) is not intended for use as an antihypertensive drug.

10.2 Pharmacodynamics

The pharmacokinetics of tamsulosin have been evaluated in adult healthy volunteers and patients with BPH with doses ranging from 0.1 mg to 1 mg.

10.3 Pharmacokinetics

Absorption: Absorption of tamsulosin from the tamsulosin 0.4 mg sustained-release formulation is essentially complete (>90%) following oral administration under fasted conditions. Time to maximum concentration (T_{max}) is reached by four to five hours under fasted conditions and by six to seven hours when tamsulosin is administered with food. The delay in T_{max} when tamsulosin is administered with food has the desirable effect of smoothing the tamsulosin plasma concentration profile, thereby reducing fluctuation of the plasma peak and trough concentrations with multiple dosing. Taking tamsulosin under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentration (C_{max}) compared to fed conditions. The effects of food on the pharmacokinetics of tamsulosin are consistent regardless of whether tamsulosin is taken with a light breakfast or a high fat breakfast (Table 5).

Table 5: Mean Pharmacokinetic Parameters Following Daily (Q.D.) Dosing with Tamsulosin 0.4 mg Once Daily or 0.8 mg Once Daily Dosing with a Light Breakfast, High Fat Breakfast or Fasted.

Pharmacokinetic Parameter	0.4 mg q.d. to healthy volunteers (age range 18-32 years)		0.8 mg q.d. to healthy volunteers (age range 55-75 years)		
	Light Breakfast	Fasted	Light Breakfast	High Fat Breakfast	Fasted
AUC (ng·hr/mL)	151	199	440	449	557
T_{max} (hours)[1]	6.0	4.0	7.0	6.5	5.0
C_{max} (ng/mL)	10.1	17.1	29.8	29.1	41.6
C_{min} (ng/mL)	3.8	4.0	12.3	13.5	13.3
C_{max}/C_{min} Ratio	3.1	5.3	2.7	2.5	3.6

AUC : area under the tamsulosin plasma time curve over the dosing interval;
T_{max}: median time-to-maximum concentration;
C_{max}: observed maximum tamsulosin plasma concentration;
C_{min}: observed minimum concentration.
Coefficients of variation (% CV) for C_{max} and AUC generally ranged from 35%-53%, collectively.
[1] median

Distribution: The mean steady-state apparent volume of distribution of tamsulosin after intravenous administration to ten healthy male adults was 16 liters, 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, gallbladder, 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 radiolabeled 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 Sandoz Tamsulosin 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 Sandoz Tamsulosin formulation, the apparent half-life of tamsulosin increases to approximately 9 to 13 hours in healthy volunteers and to 14 to 15 hours in the target population.

Special Populations and Conditions

- **Pediatrics:** Sandoz Tamsulosin 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:** Cross-study comparisons of tamsulosin overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. However, tamsulosin has been found to be a safe and effective $alpha_1$ adrenoreceptor antagonist when administered at therapeutic doses (0.4 mg and 0.8 mg once daily) to patients over the age of 65 years.
- **Sex:** Sandoz Tamsulosin 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 Sandoz Tamsulosin 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 Sandoz Tamsulosin 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 – 30°C), protect from heat and moisture.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

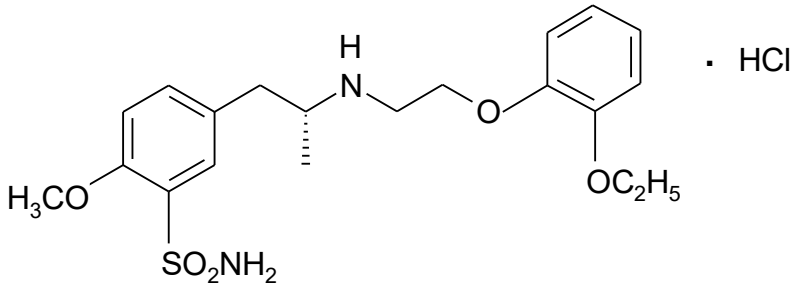
Drug Substance

Proper name: Tamsulosin hydrochloride

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

Molecular formula and molecular mass: $C_{20}H_{28}N_2O_5S{\cdot}HCl$; 445.0 g/mol

Structural formula:



Physicochemical properties:

Tamsulosin hydrochloride is a white or almost white powder. The melting range is 228- 230 °C. It is slightly soluble in water, sparingly soluble in ethanol and methanol, insoluble in non-polar organic solvents (hexane).

Solubility:

	Solubility (mg/mL)	
Solvent Media	25 °C	37 °C
water	7.8	9.2
0.1M HCl, pH 1.2	1.7	3.7
0.15 M phosphate buffer, pH 3.0	7.3	9.5
0.15 M phosphate buffer, pH 6.8	8.1	7.8
0.15 M phosphate buffer, pH 8.0	2.1	1.4
ethanol	0.12	-

pH (1% tamsulosin solution): 4.8 – 5.3

pH (7.5 mg/mL): 5.20

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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

Four large placebo-controlled clinical studies and one large active-controlled clinical study comprising 2296 patients (1003 received tamsulosin 0.4 mg once daily, 491 received tamsulosin 0.8 mg once daily, and 802 were control patients) were conducted in the U.S. and Europe. These studies support the once daily tamsulosin dose of 0.4 mg and 0.8 mg.

Tamsulosin was extensively studied in two U.S. placebo-controlled, double-blind, 13-week, multicenter studies (Study 1 and Study 2) that included 1486 men with the signs and symptoms of BPH. The validated Total AUA Symptom Score questionnaire evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Decreases in scores are consistent with improvements in symptoms.

Peak urine flow rate was measured at all visits, and increased peak urine flow rate values over Baseline are consistent with decreased urinary obstruction.

In Study 1, peak urine flow rate was measured during the estimated time of peak plasma concentration (4 to 8 hours after dosing). In Study 2, peak urine flow rate was measured at the estimated time of peak plasma concentration for the first two weeks of the double-blind treatment (4 to 8 hours after dosing), and at the estimated time of trough plasma concentration (24 to 27 hours after dosing) thereafter. In both studies, patients were randomized to either placebo, tamsulosin 0.4 mg once daily or tamsulosin 0.8 mg once daily groups. Patients in tamsulosin 0.8 mg once daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8 mg once daily dose

Table 6 Mean Changes from Baseline to Endpoint in Total AUA Symptom Score (0-35) and Peak Urine Flow Rate (mL/sec)

	Total AUA Symptom Score		Peak Urine Flow Rate	
	Mean Baseline Value	**Mean Change**	**Mean Baseline Value**	**Mean Change**
Study 1 †				
Tamsulosin 0.8 mg once daily	19.9 n=247	-9.6* n=237	9.57 n=247	1.78* n=247
Tamsulosin 0.4 mg once daily	19.8 n=254	-8.3* n=246	9.46 n=254	1.75* n=254
Placebo	19.6 n=254	-5.5 n=246	9.75 n=254	0.52 n=253
Study 2 ††				
Tamsulosin 0.8 mg once daily	18.2 n=244	-5.8* n=238	9.96 n=244	1.79* n=237
Tamsulosin 0.4 mg once daily	17.9 n=248	-5.1* n=244	9.94 n=248	1.52 n=244
Placebo	19.2 n=239	-3.6 n=235	9.95 n=239	0.93 n=235

* Statistically significant difference from placebo (p-value ≤0.050; Bonferroni-Holm multiple test procedure)

† Peak urine flow rate measured 4 to 8 hours post dose at endpoint

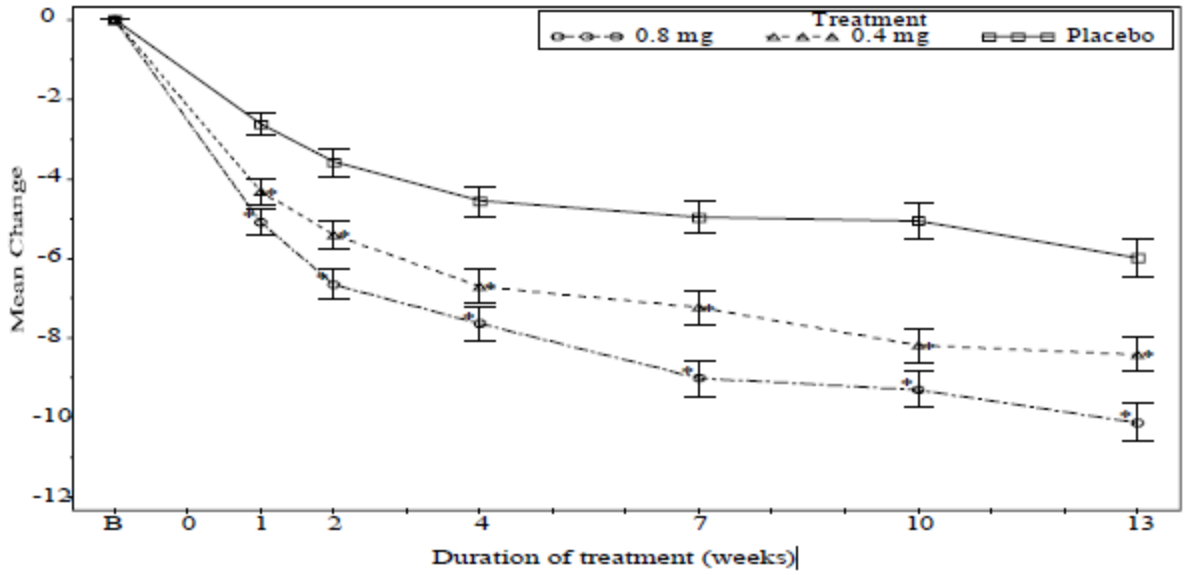
†† Peak urine flow rate measured 24 to 27 hours post dose at endpoint

Mean Total AUA Symptom Score at Endpoint was improved relative to Baseline in Study 1 and Study 2 in both tamsulosin treatment groups (Table 6). Both treatment groups were statistically significantly improved (p-value ≤ 0.050) compared to placebo.

At the initial evaluation one week after dosing, a reduction in symptoms had occurred, with significant improvements from Baseline compared to placebo in the mean Total AUA Symptom Score in both tamsulosin treatment groups for Study 1 (Figure 1). The improvements persisted for the duration of the study.

Figure 1 Mean (±S.E.) Change from Baseline in Total AUA Symptom Score (0-35)

Study 1

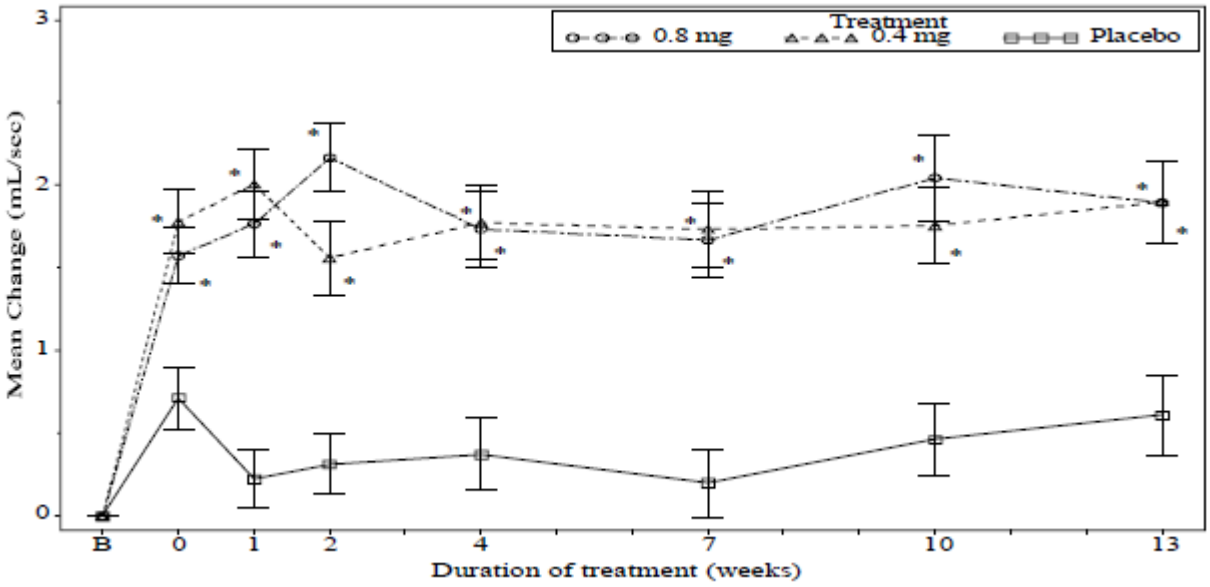


* indicates significant difference from placebo (p-value ≤ 0.050).
B=Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Total AUA Symptom Scores range from 0 to 35.

Patients treated with tamsulosin had an increase in peak urine flow rate that was statistically significant (p-value ≤ 0.050) 4 to 8 hours after the initial dose of therapy (Figure 2). This improvement in the patients treated with tamsulosin was also evident throughout the duration of clinical studies in both the 0.4 mg once daily and 0.8 mg once daily dosing groups.

FIGURE 2 Mean (±S.E.) Increase in Peak Urine Flow Rate (mL/sec)

Study 1



* indicates significant difference from placebo (p-value ≤ 0.050).
B=Baseline determined approximately one week prior to the initial dose of double-blind medication at week 0.
Note: The uroflowmetry assessments at week 0 were recorded four to eight hours after patients received the first dose of double-blind medication.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.

Patients in this study completed a validated Quality of Life assessment questionnaire covering the following topics: "physical discomfort," "worry about health," "bothersomeness of condition," and "time kept from doing things". Both tamsulosin treatment groups experienced statistically significant (p-value ≤ 0.050) improvements from Baseline to Endpoint compared with patients in the placebo treatment group. A subgroup analysis of the effect of tamsulosin on blood pressure of normotensive patients and uncontrolled hypertensive patients did not reveal any clinically significant blood pressure lowering effect of tamsulosin 0.4 or 0.8 mg once daily compared with placebo (Table 7). A similar lack of blood pressure lowering effect was also seen in controlled hypertensives (Baseline diastolic blood pressure < 90 mmHg).

Table 7: Mean Change in Blood Pressure (mmHg) From Baseline to Final Visit in Study 1

		Normotension			Hypertension (Uncontrolled)*		
	Treatments	**n**	**Mean Baseline Value**	**Mean Change**	**n**	**Mean Baseline Value**	**Mean Change**
Systolic Blood Pressure (mmHg)	Tamsulosin 0.8 mg once daily	170	127	-1.9	40	146	-10.2
	Tamsulosin 0.4 mg once daily	182	127	-2.7	37	145	-7.2
	Placebo	172	127	1.3	41	147	-8.4
Diastolic Blood Pressure (mmHg)	Tamsulosin 0.8 mg once daily	170	80	0.1	40	96	-8.5
	Tamsulosin 0.4 mg once daily	182	80	0.0	37	96	-7.2
	Placebo	172	80	1.2	41	98	-8.6

*Hypertensive patients whose average of the last two diastolic measurements in the sitting position during the single-blind placebo evaluation period regardless of the treatment the patient was taking was ≥ 90mmHg.

A total of 1547 patients with the signs and symptoms of BPH involved in the U.S. and European short-term trials continued therapy with tamsulosin in controlled and uncontrolled follow-up studies examining long-term efficacy and safety which support the use of tamsulosin for over one year in the treatment of BPH.

Results from a long-term, U.S. placebo-controlled, double-blind extension of Study 1 showed that, in the 269 patients treated with tamsulosin, both Total AUA Symptom Score and Peak Urine Flow Rate continued to show improvement (p-value ≤ 0.050) from Baseline for one year.

14.2 Comparative Bioavailability Studies

A single dose (1 x 0.4 mg), crossover, comparative bioavailability study of Sandoz Tamsulosin and Flomax® was conducted in healthy male volunteers under fasting conditions. Data from the 21 subjects who completed the study are summarised in the table below.

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)	161.21 177.57 (51.60)	152.77 163.66 (36.67)	105.5	95.2 - 117.0
AUC_I (ng·h/mL)	165.69 183.50 (53.89)	157.11 168.35 (36.73)	105.5	94.9 - 117.2
C_{max} (ng/mL)	12.90 13.37 (26.72)	12.46 13.49 (38.08)	103.5	89.0 - 120.4
T_{max}[3] (h)	4.45 (17.00)	5.38 (49.13)		
$T_{½}$[3] (h)	10.40 (20.08)	10.40 (18.72)		

[1] Sandoz Tamsulosin (tamsulosin hydrochloride) sustained-release capsules, 0.4 mg (Sandoz Canada Inc.)
[2] Flomax® (tamsulosin hydrochloride) sustained-release capsules, 0.4 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the arithmetic mean (CV%) only

A single dose (1 x 0.4 mg) crossover, comparative bioavailability study of Sandoz Tamsulosin and Flomax® was conducted in healthy male volunteers under fed conditions (high-fat high-calorie). Data from the 20 subjects who completed the study are summarised below.

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)	155.25 164.48 (37.12)	159.81 171.81 (40.78)	97.1	89.4 - 105.6
AUC_I (ng·h/mL)	163.26 174.94 (41.63)	167.20 181.59 (44.32)	97.6	89.9 - 106.1

Tamsulosin (1 x 0.4 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
C_{max} (ng/mL)	8.95 9.489 (37.49)	8.34 8.86 (38.09)	107.4	93.6 - 123.1
T_{max}[3] (h)	7.05 (42.61)	10.1 (56.65)		
$T_{½}$[3] (h)	11.99 (29.96)	11.24 (25.77)		

[1] Sandoz Tamsulosin (tamsulosin hydrochloride) sustained-release capsules, 0.4 mg (Sandoz Canada Inc.)
[2] Flomax® (tamsulosin hydrochloride) sustained-release capsules, 0.4 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the arithmetic mean (CV%) only

A multiple dose, crossover, comparative bioavailability study of Sandoz Tamsulosin daily for 7 consecutive days (total dose of 2.8 mg) and Flomax® was conducted in healthy male volunteers under fasting conditions. Data from the 25 subjects who completed the study are summarized in the table below.

Tamsulosin (1 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)	187.62 205.13 (42.98)	205.36 225.85 (43.54)	91.4	83.4 - 100.0
C_{max} (ng·h/mL)	17.82 18.94 (34.57)	18.86 20.11 (36.20)	94.5	85.7 - 104.3
C_{min} (ng/mL)	3.29 3.86 (57.98)	3.64 4.24 (54.19)	90.5	80.9 - 101.3
T_{max}[3] (h)	3.42 (24.85)	4.67 (19.95)		
FI[3] (%)	188.26 (25.05)	180.24 (26.62)		

[1] Sandoz Tamsulosin (tamsulosin hydrochloride) sustained-release capsules, 0.4 mg (Sandoz Canada Inc.)
[2] Flomax® (tamsulosin hydrochloride) sustained-release capsules, 0.4 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

See 10 CLINICAL PHARMACOLOGY.

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 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. Pr Flomax®, sustained-release capsules, 0.4 mg, submission control 114264, Product Monograph, Boehringer Ingelheim (Canada) Ltd. AUG 15, 2007.
2. Pr Flomax® CR, tablets, controlled release, 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]Sandoz® Tamsulosin

Tamsulosin Hydrochloride Sustained-release Capsules

Read this carefully before you start taking **Sandoz Tamsulosin** 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 **Sandoz Tamsulosin**.

What is Sandoz Tamsulosin used for?

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

How does Sandoz Tamsulosin work?

Sandoz Tamsulosin 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 Sandoz Tamsulosin?

Medicinal ingredient: Tamsulosin hydrochloride

Non-medicinal ingredients: methacrylic acid-ethyl acrylate copolymer, microcrystalline cellulose, polyacrylate, polysorbate 80, purified water, sodium lauryl sulphate and talc.

Capsule shell contains: black iron oxide, gelatine, indigo carmine, red iron oxide, titanium dioxide, yellow iron oxide.

Capsule imprinting ink contains TekPrint SW-9008 Blank Ink: black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution. Opacode Black S-1-27794: Industrial methylated spirit 74 OP, Iron oxide black JPE, Isopropyl alcohol, N-butyl alcohol, Propylene glycol, Purified water, Shellac glaze – 47.5 % (22 % esterified) IN IMS 74 OP

Sandoz Tamsulosin comes in the following dosage forms:

Sustained-release capsules containing 0.4 mg tamsulosin hydrochloride.

Do not use Sandoz Tamsulosin if:

- you are allergic to tamsulosin or any of the other ingredients in Sandoz Tamsulosin or any part of the container.
- you are taking ketoconazole (an antifungal used to treat fungal skin infection).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Tamsulosin. 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 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:**
    - Sandoz Tamsulosin may cause dizziness. Do NOT drive, use machines or perform hazardous tasks for 12 hours after taking Sandoz Tamsulosin, or until you know how it affects you.
- **Fainting:**
    - Sandoz Tamsulosin 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 Sandoz Tamsulosin, you must have regular checkups. Follow your healthcare professional’s advice about when to have these checkups.
- **Sandoz Tamsulosin 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 Sandoz Tamsulosin, 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 Sandoz Tamsulosin 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 Sandoz Tamsulosin 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 Sandoz Tamsulosin:

- medicines used to lower blood pressure
  - Taking Sandoz Tamsulosin 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 Sandoz Tamsulosin:

- Take Sandoz Tamsulosin exactly as your healthcare professional has told you.

- Swallow Sandoz Tamsulosin capsules whole. Do NOT crush, chew or open Sandoz Tamsulosin capsules.
- This medicine has been prescribed specifically for you. Do NOT give your Sandoz Tamsulosin 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 Sandoz Tamsulosin again.
- Sandoz Tamsulosin should be taken approximately one-half hour following the same meal each day.

Usual dose:

You should take one capsule (0.4 mg) once a day following the same meal every day.

Overdose:

If you think you, or a person you are caring for, have taken too much Sandoz Tamsulosin, 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 Sandoz Tamsulosin 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 Sandoz Tamsulosin?

These are not all the possible side effects you may have when taking Sandoz Tamsulosin. 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,			✓

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**	
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 – 30°C), protect from heat and moisture.

Keep out of reach and sight of children.

If you want more information about Sandoz Tamsulosin:

- 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.sandoz.ca), or by calling the manufacturer, Sandoz Canada Inc., at: 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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