PRODUCT MONOGRAPH

Pr pms-SILODOSIN
Silodosin Capsules

4 mg and 8 mg

Selective antagonist for $ALPHA_{1A}$ Adrenoreceptor subtype in the prostate and bladder

ATC code: G04C A04

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Silodosin Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All nonmedicinal ingredients
Oral	Capsule, Immediate-Release, 8 mg and 4 mg	Butylhydroxytoluene, Magnesium Aluminometasilicate, Magnesium Stearate, Mannitol, Pregelatinized Starch, Polysorbate 80. Capsules contains: Gelatin and Titanium Dioxide. The markings on the capsules are in black ink, which contains Shellac, Black Iron Oxide, Propylene Glycol, Potassium Hydroxide and Water.

INDICATIONS AND CLINICAL USE

pms-SILODOSIN (silodosin) is indicated for:

- the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Geriatrics (≥ 65 years of age):
Silodosin has been found to be safe and effective when administered at therapeutic doses (8 mg once daily) to patients over the age of 65 years (see CLINICAL TRIALS section).

Pediatrics (< 18 years of age):
The safety and effectiveness of silodosin in pediatric patients have not been established. pms-SILODOSIN is not indicated for use in children (see WARNINGS AND PRECAUTIONS section).

Women:
The safety and effectiveness of silodosin in female patients have not been established. pms-SILODOSIN is not indicated for use in women (see WARNINGS AND PRECAUTIONS section).

CONTRAINDICATIONS

- pms-SILODOSIN (silodosin) is contraindicated in patients known to have hypersensitivity to silodosin or any component of the pms-SILODOSIN formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- pms-SILODOSIN should not be administered to patients with severe hepatic impairment (Child-Pugh scores ≥ 10) (see WARNINGS AND PRECAUTIONS section).
- pms-SILODOSIN should not be administered to patients with severe renal impairment (CCr < 30 mL/min) (see WARNINGS AND PRECAUTIONS section).
- pms-SILODOSIN should not be administered to patients using concomitant potent CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir) (see WARNINGS AND PRECAUTIONS section).
- pms-SILODOSIN should not be administered to patients using concomitant alpha-blockers (e.g., prazosin, terazosin, doxazosin) (see WARNINGS AND PRECAUTIONS section).

WARNINGS AND PRECAUTIONS

As with all α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with silodosin, 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 (see WARNINGS AND PRECAUTIONS, Cardiovascular section and ADVERSE REACTIONS section).

Patients beginning treatment with pms-SILODOSIN should be cautioned to avoid situations where injury could result should syncope occur.

General

Prostatic carcinoma: Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Therefore, patients thought to have BPH should be examined prior to starting therapy with pms-SILODOSIN to rule out the presence of carcinoma of the prostate.

Carcinogenesis and Mutagenesis

Carcinogenicity and mutagenicity studies have been performed in animals (see TOXICOLOGY section).

Cardiovascular

pms-SILODOSIN is not indicated for the treatment of hypertension.

Orthostatic hypotension, with or without symptoms (e.g., dizziness) may develop when beginning silodosin treatment. As with other alpha-blockers, there is potential for syncope. Patients should be cautioned about driving, operating machinery, or performing hazardous tasks when initiating

therapy.

pms-SILODOSIN should not be administered to patients using concomitant alpha-blockers. pms-SILODOSIN should be administered with caution to patients using other concomitant pharmaceuticals known or suspected of inducing orthostatic hypotension or syncope (see ADVERSE REACTIONS, Vascular Disorders section and DRUG INTERACTIONS, Drug-Drug Interactions section).

Endocrine and Metabolism
pms-SILODOSIN should not be administered to patients using concomitant potent CYP3A4 inhibitors.

Hepatic
pms-SILODOSIN should not be administered to patients with severe hepatic insufficiency (Child-Pugh scores ≥ 10).

Ophthalmologic
Intraoperative Floppy Iris Syndrome has been observed during cataract surgery in some patients on alpha-1 blockers or previously treated with alpha-1 blockers. 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. Patients planning cataract surgery should be told to inform their ophthalmologist that they are taking pms-SILODOSIN.

Renal
pms-SILODOSIN should not be administered to patients with severe renal insufficiency (CCr < 30 mL/min). In patients with moderate renal impairment (CCr 30 - 50 mL/min), the dose should be reduced to 4 mg once daily taken with a meal. No dosage adjustment is needed in patients with mild renal impairment (CCr 50-80 mL/min).

Special Populations

Pregnant Women:
pms-SILODOSIN is not indicated nor recommended for use in women. No embryotoxic and/or teratogenic effects in rats or rabbits were observed with silodosin.

Nursing Women:
pms-SILODOSIN is not indicated nor recommended for use in women. It is unknown if the drug is excreted in human milk.

Pediatrics (< 18 years of age):
pms-SILODOSIN is not indicated for use in children.

Geriatrics (≥ 65 years of age):
In double-blind, placebo-controlled, 12-week clinical studies of silodosin, 259 (55.6%) patients

were under 65 years of age, 207 (44.4%) patients were 65 years of age and over, while 60 (12.9%) patients were 75 years of age and over. Orthostatic hypotension was reported in 2.3% of silodosin patients < 65 years of age (1.2% for placebo), 2.9% of silodosin patients ≥ 65 years of age (1.9% for placebo), and 5.0% of patients ≥ 75 years of age (0% for placebo). There were otherwise no significant differences in safety or effectiveness between older and younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Retrograde ejaculation and dizziness are the most frequent adverse events with silodosin. Retrograde ejaculation is reversible upon discontinuation of the drug.

Clinical Trial Adverse Drug Reactions

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

In U.S. Phase 3 clinical trials, 897 patients with BPH were exposed to 8 mg silodosin daily. This includes 486 patients exposed for 6 months and 168 patients exposed for 1 year. The population was 44 to 87 years of age, and predominantly Caucasian. Of these patients, 42.8% were 65 years of age or older and 10.7% were 75 years of age or older.

Safety information was derived from two U.S. Phase 3 double-blind, placebo-controlled clinical studies (Studies 1 and 2) in which 466 patients were administered silodosin and 457 patients were administered placebo. At least one treatment-emergent adverse reaction was reported by 55.2% of silodosin treated patients (36.8% for placebo treated). A total of 6.4% of silodosin treated patients (2.2% for placebo treated) discontinued therapy due to an adverse reaction (treatment-emergent), the most common reaction being retrograde ejaculation (2.8%) for silodosin treated patients. Retrograde ejaculation is reversible upon discontinuation of treatment.

The incidence of adverse treatment-emergent events listed in the following table were derived from two 12-week, multicenter, double-blind, placebo-controlled clinical studies of silodosin 8 mg daily in BPH patients. Adverse events that occurred in at least 2% of patients treated with silodosin and more frequently than with placebo are shown in Table 1.

Table 1 Adverse Treatment-Emergent Events Occurring in ≥ 2% of Patients in 12- week, Placebo-Controlled Clinical Trials

Adverse Events	Silodosin (N = 466) n (%)	Placebo (N = 457) n (%)
Retrograde Ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic Hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal Congestion	10 (2.1)	1 (0.2)

In Studies 1 and 2, treatment-related adverse events that were reported as ≥ 1% and < 2% of patients receiving silodosin and occurred more frequently than with placebo are presented in Table 2.

Table 2 Treatment-Related Adverse Events Occurring in ≥ 1% and < 2% of Patients in 12-week, Placebo-Controlled Clinical Trials

Adverse Events	Silodosin (N = 466) % of patients	Placebo (N = 457) % of patients
Nervous System Disorders Headache	6 (1.3)	1 (0.2)
Vascular Disorders Orthostatic Hypotension	9 (1.9)	7 (1.5)
Gastrointestinal Disorders Diarrhea	5 (1.1)	1 (0.2)
Respiratory Thoracic and Mediastinal Disorders Nasal Congestion	7 (1.5)	1 (0.2)

Vascular Disorders

In two U.S. Phase 3 double-blind, placebo-controlled clinical studies (Studies 1 and 2), treatment-related dizziness was seen in 2.4% of patients receiving silodosin and 0.7% of those receiving placebo.

A test for orthostatic hypotension was conducted 2 to 6 hours after the first dose in the two 12-week, double-blind, placebo-controlled clinical studies. After the patient had been at rest in a supine position for 5 minutes, the patient was asked to stand. Blood pressure and heart rate were assessed at 1 minute and 3 minutes after standing. A positive result was defined as a > 30 mmHg decrease in systolic blood pressure, or a > 20 mmHg decrease in diastolic blood pressure, or a > 20 bpm increase in heart rate, as presented in Table 3.

Table 3 Summary of Orthostatic Test Results in 12-week, Placebo-Controlled Clinical Trials

Time of Measurement	Test Result	Silodosin (N = 466) % of patients	Placebo (N = 457) % of patients
1 Minute After Standing	Negative	459 (98.7%)	454 (99.6%)
	Positive	6 (1.3%)	2 (0.4%)
3 Minutes After Standing	Negative	456 (98.1%)	454 (99.6%)
	Positive	9 (1.9%)	2 (0.4%)

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Vascular Disorders
One case of **syncope** in a patient taking prazosin concomitantly was reported in the silodosin treatment group. In a 9-month open-label safety study, loss of consciousness was observed in one patient. Because the investigator who examined this patient could not rule out the possibility that silodosin was causative, this event was considered related to silodosin use.

Post-Market Adverse Drug Reactions

The following adverse events have been identified during post-approval use of silodosin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Eye Disorders:
Cases of Intraoperative Floppy Iris Syndrome have been reported (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Hepatobiliary Disorders:
Cases of jaundice, impaired hepatic function associated with increased transaminase values, and abnormal liver function tests have been reported.

Immune System Disorders:
Cases of allergic-type reactions, not limited to skin reactions including swollen tongue and pharyngeal edema resulting in hospitalization have been reported.

Skin and Subcutaneous Tissue Disorders:
Cases of toxic skin eruption (drug eruption), purpura, skin rash, pruritus, urticaria, angioedema, dermatitis exfoliative, swelling face, erythema and erythema multiforme have been reported.

Cardiac Disorders:
Cases of tachycardia and palpitations have been reported.

Respiratory Disorders:
Cases of dyspnoea, interstitial lung disease, eosinophilic pneumonia, and eosinophilic pneumonia (acute) have been reported.

DRUG INTERACTIONS

Overview

Silodosin is not an inducer or an inhibitor of any of the principal hepatic enzymes involved in the metabolism of other drugs.

CYP3A4 is a principal hepatic enzyme isoform involved in the metabolism of silodosin.

Potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin and ritonavir, increase silodosin blood levels and exposure (Area Under the Curve - AUC). pms-SILODOSIN should not be co-administered with potent inhibitors of CYP3A4 (see CONTRAINDICATIONS). See Drug-Drug Interactions for details of increased silodosin blood levels. As this is only a partial list, the physician is advised to consult current scientific literature regarding other CYP3A4 competitive inhibitors prior to prescribing pms-SILODOSIN if other concomitant medications are used.

Moderate CYP3A4 inhibitor diltiazem increased the silodosin AUC by approximately 30%, but the maximum concentration (C_{max}) and half-life were not affected. No dose adjustment is required.

It is not known how combined exposure of any medications metabolized by the CYP3A4 hepatic enzyme isoform (such as alpha1-blockers), herbal remedies (particularly St. John's Wort, Milk Thistle), and grapefruit juice may influence the overall efficacy and unwanted side effects of these medications. Therefore, caution should be exercised.

Strong P-glycoprotein (P-gp) Inhibitors
In vitro studies indicated that silodosin is a P-gp substrate. Ketoconazole, a CYP3A4 inhibitor that also inhibits P-gp, caused significant increase in exposure to silodosin. Inhibition of P-gp may lead to increased silodosin concentration. pms-SILODOSIN is therefore not recommended in patients taking strong P-gp inhibitors such as cyclosporine.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 Established or Potential Drug-Drug Interactions

Drug / Class	Reference	Effect	Clinical Comment
Ketoconazole, 400 mg	CT	Increased silodosin plasma concentration 3.7-fold	Recommend not using silodosin with potent CYP3A4 inhibitors.
Potent CYP3A4 Inhibitors (ritonavir)	T	Increased silodosin plasma concentration	Recommend not using silodosin with potent CYP3A4 inhibitors.
Strong P-glycoprotein (P-gp) Inhibitors (cyclosporine)	T	Increased silodosin plasma concentration	Recommend not using silodosin with potent P-gp inhibitors.
Diltiazem, 300 mg	CT	Increased silodosin plasma AUC by 30%	AUC was elevated by approximately 30%, but other parameters were not increased. No dosage adjustment needed.
Digoxin, 0.25 mg	CT	None	Seven day co-administration did

			not influence the steady state pharmacokinetics of either drug.
Sildenafil, 100 mg	CT	In subjects < 65 years of age a mean increase in heart rate was observed during orthostatic tests, while those ≥ 65 demonstrated a slight mean decrease in blood pressure.	No events of symptomatic orthostasis occurred in subjects receiving silodosin with sildenafil, nor were there any events of dizziness.
Tadalafil, 20 mg	CT	In subjects < 65 years of age a mean increase in heart rate was observed during orthostatic tests, while those ≥ 65 demonstrated a slight mean decrease in blood pressure.	No events of symptomatic orthostasis occurred in subjects receiving silodosin with tadalafil, nor were there any events of dizziness.
Antihypertensives	CT	Slightly higher incidence of adverse effects when used concomitantly	Approximately one-third of the patients in the two Phase 3 clinical studies used concomitant antihypertensive medications. The incidence of dizziness and orthostatic hypotension in these patients was higher than in the general silodosin population (4.6% versus 3.8% and 3.4% versus 3.2%, respectively). Exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events.
Alpha-1 blockers	T	Increase in orthostatic effects	The pharmacodynamic interactions may be expected, and silodosin should not be used in combination with other alpha-blockers. Nevertheless, exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events.

Legend: CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

The oral bioavailability of silodosin is not changed when taken with food. Food decreases C_{max} by approximately 30% and increases t_{max} by approximately 1 hour.

pms-SILODOSIN should be taken orally once daily with a meal.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

No laboratory test interactions were observed during clinical evaluations. Treatment with silodosin for up to 52 weeks had no significant effect on prostate-specific antigen (PSA).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Before prescribing pms-SILODOSIN, consider the following situations that may affect dosing of the drug:

- Potent CYP3A4 inhibitors (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism section)
- Hepatic insufficiency (see WARNINGS AND PRECAUTIONS, Hepatic section)
- Renal insufficiency (see WARNINGS AND PRECAUTIONS, Renal section)

Recommended Dose and Dosage Adjustment

pms-SILODOSIN (silodosin) 8 mg once daily with a meal is recommended as the dose for the treatment of the signs and symptoms of BPH.

Renal impairment:
pms-SILODOSIN is contraindicated in patients with severe renal impairment (CCr < 30 mL/min). In patients with moderate renal impairment (CCr 30 - 50 mL/min), the dose should be reduced to 4 mg once daily taken with a meal. No dosage adjustment is needed in patients with mild renal impairment (CCr 50 - 80 mL/min).

Hepatic impairment:
Silodosin has not been studied in patients with severe hepatic impairment (Child-Pugh score ≥ 10) and is therefore contraindicated in these patients. No dosage adjustment is needed in patients with mild or moderate hepatic impairment.

Missed Dose

If a dose of pms-SILODOSIN is missed, the missed dose can be taken later the same day. If a day is missed, the missed dose should be skipped, and the regular dosing schedule should be resumed.

Doses must not be doubled.

Administration

pms-SILODOSIN should be taken orally once daily with a meal.

pms-SILODOSIN capsules may also be administered by carefully opening the capsule and sprinkling the powder inside on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the powder. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Any powder/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a pms-SILODOSIN capsule is not recommended.

OVERDOSAGE

Silodosin was evaluated at doses of up to 48 mg/day in healthy male subjects. The dose- limiting adverse event was orthostatic hypotension.

Should overdose of silodosin lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by maintaining the patient in the supine position. If this measure is inadequate, administration of intravenous fluid should be considered. If necessary, vasopressors could be used, and renal function should be monitored and supported as needed. Dialysis is unlikely to be of significant benefit since silodosin is highly (97%) protein bound.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Silodosin, indicated for the treatment of benign prostatic hyperplasia (BPH), is a uroselective antagonist of post-synaptic α_{1A}-adrenoceptors located in the prostate, prostatic capsule, bladder base, bladder neck, and prostatic urethra.

Pharmacodynamics

The clinical manifestations of benign prostatic hyperplasia (BPH) are due to bladder outlet obstruction caused by anatomical (static) and functional (dynamic) factors. The static component is related to an increase in prostate size which may not cause symptoms. The dynamic component is related primarily to an increase in smooth muscle tone in the prostate, prostatic capsule, bladder

base, bladder neck, and prostatic urethra. This increased tone is mediated by the activation of α1-adrenoceptors and leads to an increased resistance to urinary voiding and the symptoms of BPH such as a hesitant, interrupted, weak stream; urgency and leaking or dribbling; and/or more frequent urination, especially at night.

The treatment effects of silodosin are related to its effects on sympathetic nervous system adrenoreceptors. These adrenoreceptors are G protein coupled transmembrane receptors that mediate catecholaminergic actions. To date, three distinct members of this family have been identified: α_{1A}, α_{1B}, and α_{1D}. α_{1A}-adrenoreceptors are expressed abundantly in the prostatic stroma, while α_{1D}-adrenoreceptors are the predominate subtype in the nasal passages, spinal cord, and human bladder. α_{1A}-adrenoreceptors and α_{1B}-adrenoreceptors are both expressed within human vascular smooth muscle. However, as patients age, the ratio between these subtypes changes with α_{1B}-adrenoreceptors becoming predominate in the vasculature, particularly in patients over 65 years of age.

Silodosin is highly selective for α1A-adrenoreceptors. Blockade of these α1A-adrenoreceptors causes smooth muscle in the prostate to relax, resulting in an improvement in urine flow and a reduction in BPH symptoms. Silodosin has a substantially lower affinity for the α1B-adrenoreceptors.

An *in vitro* study examining binding affinity of silodosin to the three subtypes of the alpha-1 adrenoreceptors (alpha-$_{1A,}$ alpha-$_{1B}$, and alpha-$_{1D}$) was conducted. The results of the study demonstrated that silodosin binds with high affinity to the alpha-1A subtype and that the α_{1A}:α_{1B} binding ratio of silodosin is extremely high (162:1), while the α_{1A}:α_{1D} binding ratio of silodosin is moderate (55:1). This is illustrated in the table below.

Table 5 Affinity for Human α1A-AR subtype and α1A-AR Subtype Selectivity of Silodosin

Test Drug	pKi Value			α_{1A}-AR Subtype Selectivity [a]	
	α_{1A}-AR	α_{1B}-AR	α_{1D}-AR	α_{1A}/α_{1B} Ratio	α_{1A}/α_{1D} Ratio
silodosin (KMD-3213)	10.4 ± 0.07	8.19 ± 0.04	8.66 ± 0.02	162	55.0

The pKi value in the table represents the mean ± S.E. of 3 runs.

a) The subtype selectivity (α1A/α1B and α1A/α1D ratios) was calculated from the ratio after converting the concentration, specifically, using 10^M [M=pKi (α_{1A}) – pKi (α_{1B} or α_{1D})]. (Example: M=10.4-8.18 = 2.21 $10^{2.21}$ = 162)

In placebo-controlled clinical studies in patients with BPH, silodosin was shown to significantly increase average urine peak flow rate (Qmax) by 30% which is observed after the first dose. These favorable urodynamic effects may have been responsible for the improvement of lower tract irritative and obstructive symptoms that were observed. The Quality of Life Index also significantly improved in the silodosin patients.

Electrocardiography

The effect of silodosin on QT interval was evaluated in a double-blind, randomized, active-(moxifloxacin) and placebo-controlled, parallel-group study in 183 healthy male subjects aged 18 to 45 years. Subjects received silodosin 8 mg, silodosin 24 mg, or placebo once daily for 5 days, or a single dose of moxifloxacin 400 mg on Day 5 only. The 24 mg dose of silodosin was selected to achieve blood levels of silodosin that may be seen in a "worst-case" scenario exposure (i.e., in the setting of concomitant renal disease or use of strong CYP3A4 inhibitors). QT interval was measured during a 24-hour period following dosing on Day 5 (at silodosin steady state).

In 183 patients analyzed, silodosin was not associated with an increase in individual corrected (QTcI) QT interval at any time during steady state measurement, while moxifloxacin, the active control, was associated with a maximum 9.59 msec increase in QTcI.

There has been no signal of Torsade de Pointes in the post-marketing experience of silodosin.

Pharmacokinetics

The pharmacokinetics of silodosin have been evaluated in adult male subjects with doses ranging from 0.1 mg to 24 mg per day. The pharmacokinetics of silodosin are linear throughout this dosage range.

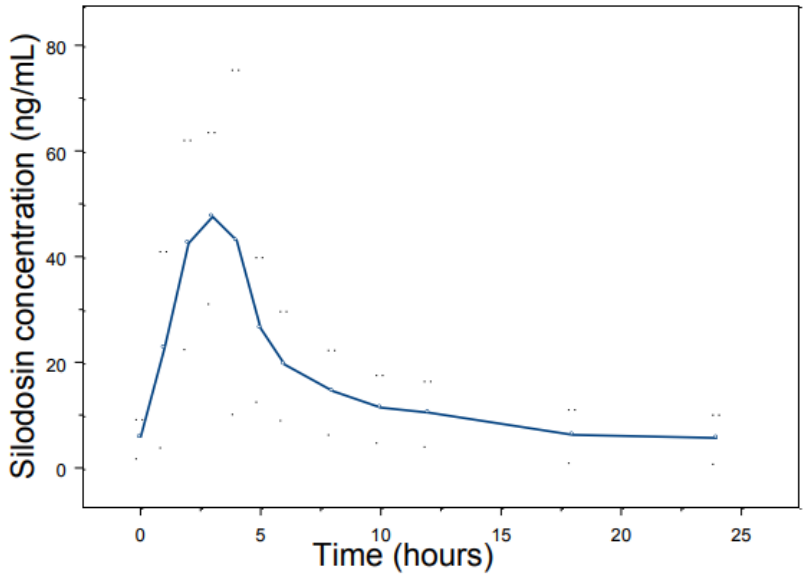
Absorption:
The pharmacokinetic characteristics of silodosin 8 mg once daily were determined in a multi-dose, open-label, 7-day pharmacokinetic study completed in 19 healthy, target-aged (≥ 45 years of age) male subjects. Table 6 and Figure 1 present the steady state pharmacokinetics of this study.

Table 6 Mean (±SD) Steady State Pharmacokinetic Parameters in Males Following Silodosin 8 mg Once Daily with a Meal

C_{max} (ng/mL)	t_{max} (hours)	$t_{1/2}$ (hours)	AUC_{ss} (ng•hr/mL)
61.6 ± 27.54	2.6 ± 0.90	13.3 ± 8.07	373.4 ± 164.94

C_{max} = maximum concentration, t_{max} = time to reach C_{max}, $t_{1/2}$ = elimination half-life, AUC_{ss} = steady state area under the concentration-time curve

Figure 1 Mean (±SD) Silodosin Steady State Plasma Concentration-Time Profile in Healthy Target-Aged Subjects following Silodosin 8 mg Once Daily with Food



The absolute bioavailability is approximately 32%.

The effect of a moderate fat, moderate calorie meal was variable and decreased silodosin C_{max} by approximately 18 - 43% and AUC by 4 - 49% across three different studies.

Distribution:
Silodosin has an apparent volume of distribution of 49.5 L and is approximately 97% protein bound.

Metabolism:
Silodosin undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 3A4 (CYP3A4) pathways. The main metabolite of silodosin is a glucuronide conjugate (KMD-3213G) that is formed via direct conjugation of silodosin by UDP-glucuronosyltransferase 2B7 (UGT2B7). Co-administration with inhibitors of UGT2B7 (e.g., probenecid, valproic acid, fluconazole) may potentially increase exposure to silodosin. KMD-3213G, which has been shown *in vitro* to be active, has an extended half-life (approximately 24 hours) and reaches plasma exposure (AUC) approximately 4 times greater than that of silodosin. The second major metabolite (KMD-3293) is formed via alcohol and aldehyde dehydrogenases and reaches plasma exposures similar to that of silodosin. KMD-3293 is not expected to contribute significantly to the overall pharmacologic activity of silodosin.

Excretion:
Following oral administration of ^{14}C-labeled silodosin, the recovery of radioactivity after 10 days was approximately 33.5% in urine and 54.9% in feces. After intravenous administration, the plasma clearance of silodosin was approximately 10 L/hour.

Special Populations and Conditions

Pediatric:
Silodosin has not been evaluated in patients less than 18 years of age.

Geriatric:
A study comparing 16 males 65 to 75 years of age, 15 males > 75 years of age, and 16 males 45 to 64 years of age was conducted. The exposure (AUC) and elimination half-life of silodosin were approximately 10% less and 17% greater, respectively, in geriatric males 65 to 75 years of age than the younger subjects, and approximately 16% less and 35% greater, respectively in geriatric males > 75 years of age than the younger subjects. A decrease in C_{max} of 13% and 40% was seen in males 65 to 75 years of age and > 75 years of age, respectively. Because of the modest degree of these changes, no dose adjustment is needed in elderly subjects (see WARNINGS AND PRECAUTIONS, Geriatrics section).

Gender:
Silodosin has not been evaluated in women.

Race:
No clinical studies specifically investigating the effects of race have been performed. However, available clinical data do not suggest clinically important differences.

Hepatic Insufficiency:
In a study comparing nine male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), to nine healthy male subjects, the single dose pharmacokinetic disposition of silodosin was not significantly altered in the patients with moderate hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of silodosin in patients with severe hepatic impairment have not been studied. pms-SILODOSIN should not be administered to patients with severe hepatic impairment (Child-Pugh scores ≥ 10).

Renal Insufficiency:
In a study with six subjects with moderate renal impairment, the total silodosin (bound and unbound) AUC, C_{max}, and elimination half-life were 3.2-, 3.1-, and 2-fold higher, respectively, compared to seven subjects with normal renal function. The unbound silodosin AUC and C_{max} were 2.0- and 1.5-fold higher, respectively, in subjects with moderate renal impairment compared to the normal controls.

In another study with eight subjects with mild and moderate renal impairment, and five subjects with severe renal impairment, the total silodosin AUC, C_{max}, and elimination half-life were 1.9-, 1.7-, and 1.3-fold higher for the mild, and 2.2-, 1.5-, and 1.7-fold higher for moderate compared to eight subjects with normal renal function. The increase in exposure to unbound silodosin was greater in patients with severe renal impairment (C_{max} and AUC 2.2- and 3.7-fold, respectively, compared to subjects with normal renal function) than in patients with moderate and mild impairment (C_{max} and AUC 1.6- and 1.8-fold, respectively).

In controlled and uncontrolled clinical studies, the incidence of orthostatic hypotension and dizziness was greater in subjects with moderate renal impairment treated with 8 mg silodosin daily than in subjects with normal or mildly impaired renal function.

pms-SILODOSIN is contraindicated in patients with severe renal impairment (CCr < 30 mL/min). In patients with moderate renal impairment (CCr 30-50 mL/min), the dose should be reduced to 4 mg once daily taken with a meal. No dosage adjustment is needed in patients with mild renal impairment (CCr 50-80 mL/min).

STORAGE AND STABILITY

Store at controlled room temperature (15°C to 30°C). Keep out of reach and sight of children. Protect from light and moisture.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each pms-SILODOSIN 4 mg capsule is white to off white colored powder filled in size “3” hard gelatin capsules with white opaque body imprinted “4 mg” and White opaque cap imprinted “M” with black ink.

Each pms-SILODOSIN 8 mg capsule is white to off white colored powder filled in size “1” hard gelatin capsules with white opaque body imprinted “8 mg” and White opaque cap imprinted “M” with black ink.

Composition:

Each pms-SILODOSIN 4 mg capsule for oral administration contains 4 mg silodosin, and the following inactive ingredients: Butylhydroxytoluene, Magnesium Aluminometasilicate, Magnesium Stearate, Mannitol, Pregelatinized Starch, Polysorbate 80. Capsules contains: Gelatin and Titanium dioxide. The markings on the capsules are in black ink, which contains Shellac, Black Iron Oxide, Propylene Glycol, Potassium Hydroxide and Water.

Each pms-SILODOSIN 8 mg capsule for oral administration contains 8 mg silodosin, and the following inactive ingredients: Butylhydroxytoluene, Magnesium Aluminometasilicate, Magnesium Stearate, Mannitol, Pregelatinized Starch, Polysorbate 80. Capsules contains: Gelatin and Titanium dioxide. The markings on the capsules are in black ink, which contains: Shellac, Black Iron Oxide, Propylene Glycol, Potassium Hydroxide and Water.

Packaging:
pms-SILODOSIN 4 mg capsule is available in blisters of 50 capsules, and bottles of 30 and 90 capsules.

pms-SILODOSIN 8 mg capsule is available in blisters of 100 capsules, and bottles of 30 and 90 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

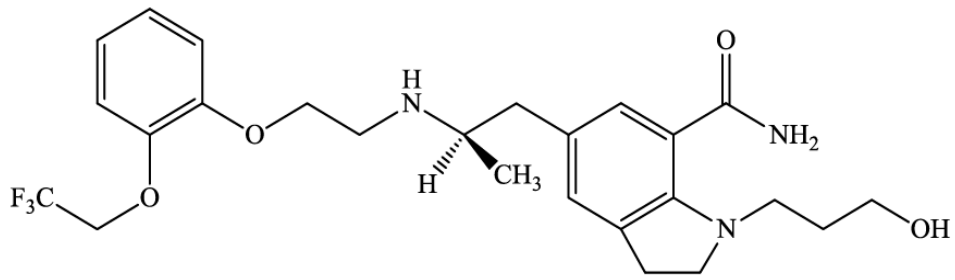
Proper Name: Silodosin

Chemical name: (-)-(R)-1-(3-Hydroxypropyl)-5-[2-({2-[2-(2,2,2-trifluoroethoxy)-phenoxy]ethyl}amino)propyl]-Indoline-7-carboxamide.

Molecular formula: $C_{25}H_{32}F_3N_3O_4$

Molecular mass: 495.53 g/mol

Structural formula:



Physiochemical properties:

Description: White to pale yellowish white powder

Melting point: Approximately 105 to 109°C.

Solubility: Freely soluble in glacial acetic acid and absolute alcohol, soluble in methanol and insoluble water.

CLINICAL TRIALS

Comparative Bioavailability Study

A randomized, double blind, balanced, single-dose, two-treatment, two-sequence, two-period, crossover comparative bioavailability study of pms-SILODOSIN 4 mg capsules (Pharmascience Inc., Canada) was performed versus RAPAFLO® (silodosin) 4 mg capsules (Allergan Inc., Canada), in 38 normal, healthy, adult, male subjects under fasting conditions. The results are summarised in the following table:

Silodosin (1 x 4 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	292.30 309.47 (36.31)	304.66 321.01 (34.25)	95.9	88.8 - 103.6
C_{max} (ng/mL)	57.09 62.22 (46.69)	63.93 69.34 (43.76)	89.3	80.3 - 99.2
AUC_I (ng.h/mL)	301.91 318.51 (35.31)	314.26 330.20 (33.21)	96.1	89.2 – 103.5
T_{max}§ (h)	2.00 (0.50-5.00)	2.30 (0.35-5.00)		
$T_{½}$€ (h)	7.08 (35.19)	7.02 (38.89)		

* pms-SILODOSIN (silodosin) capsules, 4 mg (Pharmascience Inc.)
† PrRAPAFLO® (silodosin) capsules, 4 mg (Allergan Inc., Canada)
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Study Demographic and Trial Design

Benign Prostatic Hyperplasia (BPH):
Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted with 8 mg daily of silodosin. In these two studies, 923 patients [mean age 64.6 years; Caucasian (89.3%), Hispanic (4.9%), Black (3.9%), Asian (1.2%), Other (0.8%)] were randomized and 466 patients received silodosin 8 mg daily. The two studies were identical in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Qmax) was a secondary efficacy measure.

Study Results

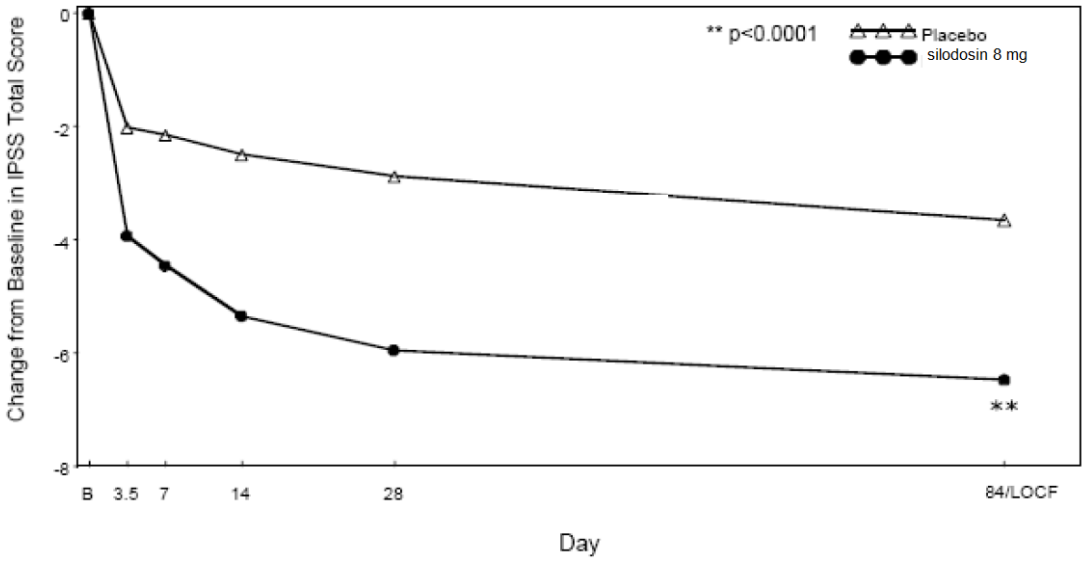
Mean changes from baseline to last assessment (Week 12) in total IPSS score were statistically significantly greater for groups treated with silodosin than those treated with placebo in both studies (Table 7 and Figure 2 and Figure 3).

Table 7 Mean Change from Baseline in International Prostate Symptom Score (IPSS) in Two Randomized, Controlled, Double-Blind Studies

Total Symptom Score	Study 1			Study 2		
	Silodosin 8 mg (n = 233)	Placebo (n = 228)	p-value	Silodosin 8 mg (n = 233)	Placebo (n = 229)	p-value
Baseline	21.5 (5.38)	21.4 (4.91)		21.2 (4.88)	21.2 (4.92)	
3 to 4 Day Change From Baseline	-3.9 (5.40)	-2.0 (4.34)	< 0.0001	-4.4 (5.12)	-2.5 (4.39)	< 0.0001
Week 12 / LOCF Change from Baseline	-6.5 (6.73)	-3.6 (5.85)	< 0.0001	-6.3 (6.54)	-3.4 (5.83)	< 0.0001

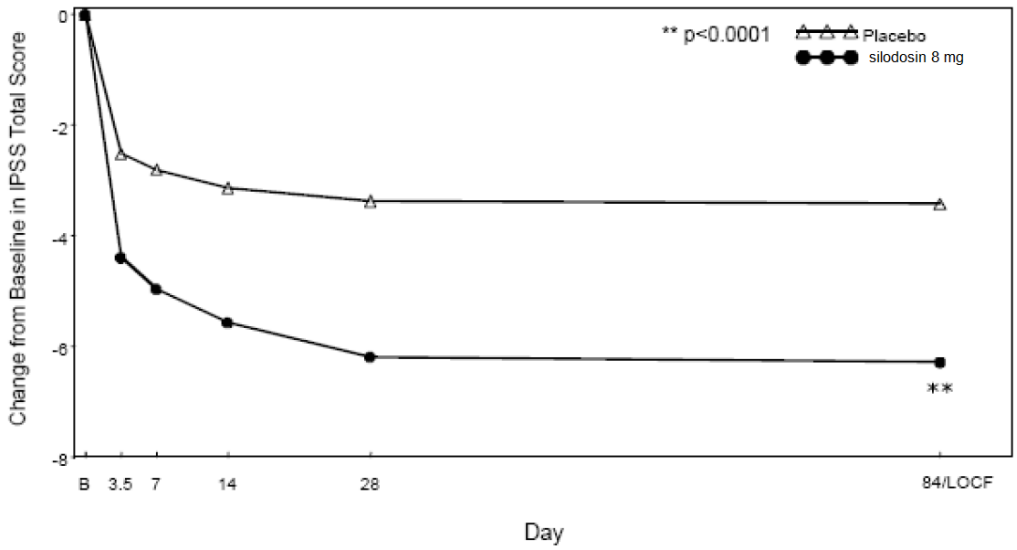
LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Figure 2 Mean Change from Baseline in IPSS Total Score by Treatment Group and Visit in Study 1



B – Baseline determination taken Day 1 of the study before the initial dose. Subsequent values are observed cases except for LOCF values.
LOCF – Last observation carried forward for those not completing 12 weeks of treatment.

Figure 3 Mean Change from Baseline in IPSS Total Score by Treatment Group and Visit in Study 2



B – Baseline determination taken Day 1 of the study before the initial dose. Subsequent values are observed cases except for LOCF values.
LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Silodosin produced highly significant reductions ($p < 0.0001$) of total IPSS scores at all time points in the studies, demonstrating both rapid (within 3 to 4 days) and sustained positive effects.

Silodosin produced significant, rapid, and sustained reductions in both irritative and obstructive symptoms as measured by the change from baseline in the appropriate IPSS subscales. Table 8 and Table 9 present IPSS irritative and obstructive subscale results.

Table 8 Mean Change (SD) from Baseline in the IPSS Irritative Symptoms Subscale in Two Randomized, Controlled, Double-Blind Studies

Irritative Symptom Score	Study 1			Study 2		
	Silodosin 8 mg (n = 233)	Placebo (n = 228)	p-value	Silodosin 8 mg (n = 233)	Placebo (n = 229)	p-value
Baseline	9.5 (2.56)	9.4 (2.44)		9.2 (2.62)	9.2 (2.59)	
3 to 4 Day Change from Baseline	-1.3 (2.42)	-0.8 (2.17)	0.0192	-1.5 (2.29)	-0.9 (2.15)	0.0033
Week 12 / LOCF Change from Baseline	-2.3 (2.97)	-1.4 (2.70)	0.0004	-2.4 (2.89)	-1.3 (2.62)	0.0001

LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Table 9 Mean Change (SD) from Baseline in the IPSS Obstructive Symptoms Subscale in Two Randomized, Controlled, Double-Blind Studies

Obstructive Symptom Score	Study 1			Study 2		
	Silodosin 8 mg (n = 233)	Placebo (n = 228)	p-value	Silodosin 8 mg (n = 233)	Placebo (n = 229)	p-value
Baseline	12.0 (3.85)	12.0 (3.57)		12.0 (3.26)	11.9 (3.49)	
3 to 4 Day Change from Baseline	-2.6 (3.57)	-1.2 (2.91)	< 0.0001	-2.9 (3.53)	-1.6 (3.06)	< 0.0001
Week 12 / LOCF Change from Baseline	-4.2 (4.32)	-2.2 (3.75)	< 0.0001	-3.9 (4.31)	-2.1 (3.77)	< 0.0001

LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

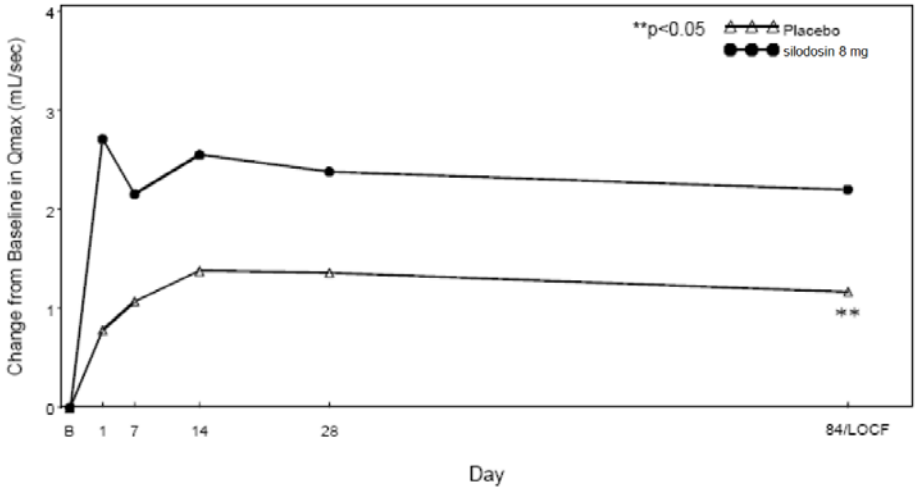
Silodosin produced rapid and significant increases in maximum urinary flow rates from baseline to last assessment versus placebo in both studies (Table 10 and Figure 4 and Figure 5). Statistically significant treatment effects on maximum urine flow rates were noted within 2 to 6 hours after the first dose and at the end of both Study 1 and 2.

Table 10 Mean Change (SD) from Baseline in Maximum Urinary Flow Rate (mL/sec) in Two Randomized, Controlled, Double-Blind Studies

Mean Maximum Flow Rate (mL/sec)	Study 1			Study 2		
	Silodosin 8 mg (n = 233)	Placebo (n = 228)	p-value	Silodosin 8 mg (n = 233)	Placebo (n = 229)	p-value
Baseline	9.0 (2.60)	9.0 (2.85)		8.4 (2.48)	8.7 (2.67)	
2 to 6 Hours Change from Baseline	2.7 (3.48)	0.8 (3.05)	< 0.0001	2.9 (3.41)	2.1 (4.26)	0.0494
Week 12 / LOCF Change from Baseline	2.2 (4.31)	1.2 (3.81)	0.0060	2.9 (4.53)	1.9 (4.82)	0.0431

LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Figure 4 Mean Change from Baseline in Qmax (mL/sec) by Treatment Group and Visit in Study 1



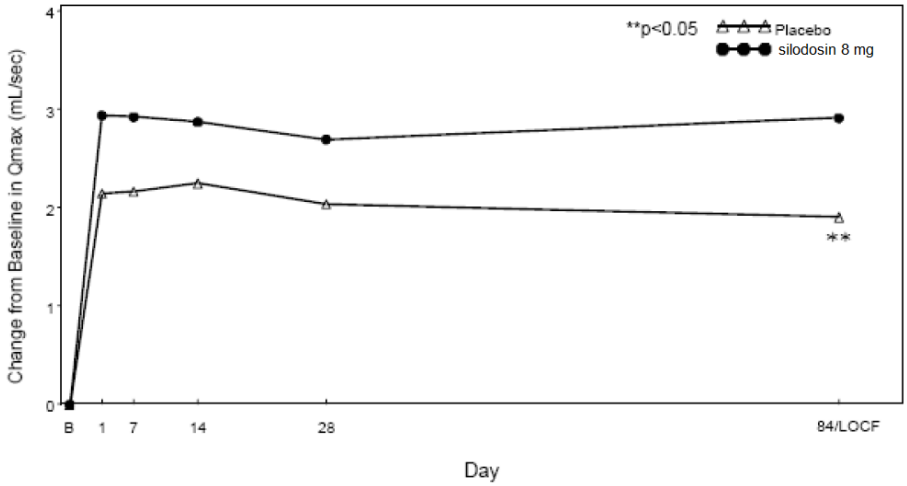
B – Baseline determination taken Day 1 of the study before the initial dose. Subsequent values are observed cases except for LOCF values.

LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Note – The first Qmax assessments at Day 1 were taken 2-6 hours after patients received the first dose of double-blind medication.

Note – Measurements at each visit were scheduled 2-6 hours after dosing (approximate peak plasma silodosin concentration).

Figure 5 Mean Change from Baseline in Qmax (mL/sec) by Treatment Group and Visit in Study 2



B – Baseline determination taken Day 1 of the study before the initial dose. Subsequent values are observed cases except for LOCF values.

LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Note – The first Qmax assessments at Day 1 were taken 2-6 hours after patients received the first dose of double-blind medication.

Note – Measurements at each visit were scheduled 2-6 hours after dosing (approximate peak plasma silodosin concentration).

Silodosin had positive effects on quality of life based on the IPSS Quality of Life subscale, as measured at various intervals during dosing. The Silodosin treatment effects exceeded treatment effects of placebo. The percentage of Silodosin patients reporting to be in the *delighted*, *pleased*, *mostly satisfied*, and *mixed* categories increased from 6.9% to 32%, whereas the percentage of placebo patients using these descriptors increased from 7.2% to 22.5%.

Table 11 Summary of Quality of Life Related to Urinary Symptoms in Two Randomized, Controlled, Double-Blind Studies

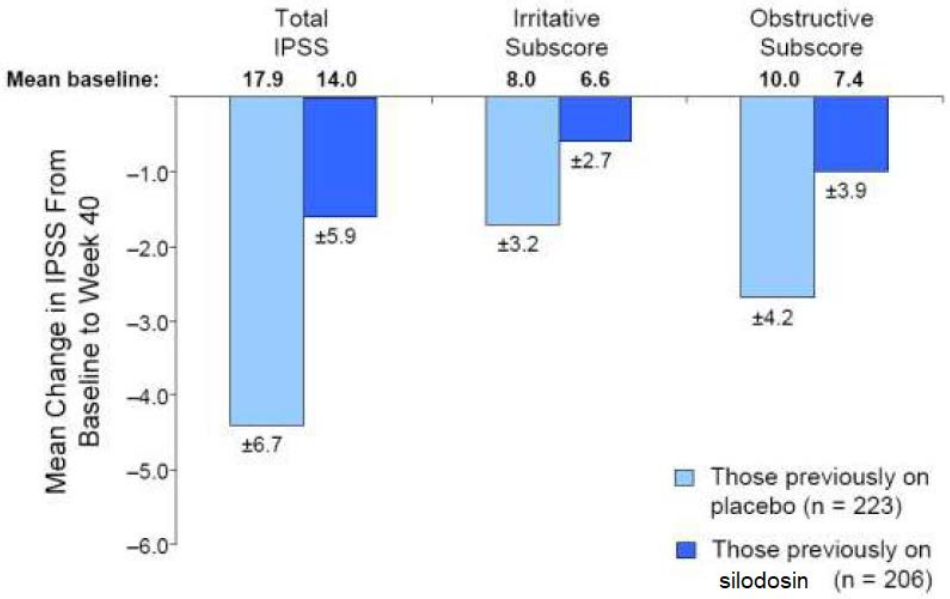
IPSS Question 8 Responses	Treatment, n (%)	
	Silodosin (n = 466)	Placebo (n = 457)
Baseline		
Delighted, pleased, or mostly satisfied	32 (6.9)	33 (7.2)
Mixed about equally satisfied and dissatisfied	126 (27.0)	124 (27.1)
Mostly dissatisfied, unhappy, or terrible	308 (66.1)	300 (65.6)
Week 12 (LOCF)		
Delighted, pleased, or mostly satisfied	149 (32.0)	103 (22.5)
Mixed about equally satisfied and dissatisfied	141 (30.3)	110 (24.1)
Mostly dissatisfied, unhappy, or terrible	176 (37.3)	244 (53.4)

LOCF – Last observation carried forward for those not providing data at 12 weeks of treatment.

Long Term Treatment of BPH

Patients in Studies 1 and 2 who received either Silodosin or placebo were allowed to continue in a 40-week open-label extension study. Patients who received silodosin in the double-blind period continued to see improvements in total IPSS as well as irritative and obstructive symptoms for up to 1 year of treatment; total IPSS score decreased by an additional 1.6 in these patients. Figure 6 provides results for all patients in the open-label extension study.

Figure 6 Mean Change (SD) from Baseline (End of Double-Blind Studies) to Week 40 in IPSS Total Score and Subscores in Open-Label Extension Study (Evaluable Population, N = 429)



DETAILED PHARMACOLOGY

Silodosin has high affinity for α1A-Adrenergic Receptor (α_{1A}-AR) subtype (pKi value: 10.4). The selectivity of silodosin for α_{1A}-AR subtype was 162 times and 55.0 times higher than for subtypes α_{1B}-AR and α_{1D}-AR, respectively. In addition, the selectivity of silodosin for subtype α1A-AR was the highest among other α1-AR blockers, including tamsulosin hydrochloride, prazosin hydrochloride, and terazosin hydrochloride. Silodosin had a strong inhibitory effect on contraction induced by treatment with noradrenalin in the lower urinary tract organs such as the prostate, the urethra and the trigone of the urinary bladder on which subtype α1A-ARs are predominantly located (the pA_2 or pK_b value: 9.60, 8.71 and 9.35, respectively). The pA_2 values of the inhibitory effect on contraction induced by treatment with noradrenalin in the isolated spleen of rats on which α1B-AR subtype is predominantly located, and in isolated thoracic aortas in rats on which α_{1D}-AR is predominantly located, were 7.15 and 7.88, respectively. The receptor binding study and the function study using isolated organs revealed that silodosin had higher selectivity for α_{1A}-AR subtype of the lower urinary tract organs compared to the other α_1- AR blockers.

In human plasma two major metabolites of silodosin (those greater than 10 percent of parent drug systemic exposure at steady state) were identified and designated KMD-3213G and KMD-3293. The glucuronide conjugate of silodosin, KMD-3213G, which is not detected in animal plasma, had 1/8 times the affinity of silodosin for human α1-AR. In animals, this human metabolite had 1/4.5 times the affinity for α_{1A}-AR subtype in rats, about 1/2 the inhibitory effect on contraction induced by noradrenalin in the isolated prostate in rats, and not greater than 1/10 the transferability to the prostate of silodosin. KMD-3293, the other major metabolite of silodosin in humans, was detected in animal plasma and had 1/42 times the affinity of silodosin for subtype α_{1A}-AR in humans.

A rat model of benign prostatic hyperplasia, prepared by administering sex hormones, had overactive bladder-like contractions when urine accumulated in the body. Silodosin significantly inhibited the number of overactive cytoid contractions. In secondary pharmacodynamic studies, silodosin had comparatively high binding affinities for β_2-AR as well as α_1-ARs, but inhibited β_2-AR in the isolated uterus in pregnant rats at a higher concentration than the concentration at which silodosin inhibited α1-ARs in the prostate. Furthermore, silodosin had low affinities for other types of receptors except for β_2-AR, and accordingly was less likely to exhibit any effects through receptor types other than α1-ARs in clinical use.

The safety pharmacology studies of silodosin revealed minimally significant effects on the central nervous system or on the respiratory system. With regard to the cardiovascular system, a decrease in blood pressure of about 20% of the baseline values was seen in conscious dogs after oral administration of silodosin at 20 mg/kg,[(1)] but silodosin had no effect on heart rate and electrocardiography in conscious dogs. Silodosin also inhibited hERG current at high concentrations and prolonged APD_{90} in the myocardial action potential in isolated papillary muscle from guinea pigs. However, these effective concentrations (4,415 ng/mL) are about 72-fold higher than 61.6 ng/mL, the maximum concentration of silodosin in healthy adult human males receiving repeat oral administration of 8 mg, which is the recommended clinical dose.

Thus, silodosin is expected to have little effect on the repolarization in the heart. In a thorough QT

electrocardiography study, silodosin capsules 8 mg daily, silodosin capsules 24 mg daily, placebo daily, or a single dose of moxifloxacin 400 mg were administered to healthy male humans. Silodosin capsules 8 mg and 24 mg daily had no statistically significant effect on ECG intervals or cardiac repolarization relative to placebo. Furthermore, there was no dose-response relationship observed with the product.

The main plasma metabolite of silodosin is a glucuronide conjugate (KMD-3213G) that is formed via direct conjugation of silodosin by UDP-glucuronosyltransferase 2B7 (UGT2B7). The second major plasma metabolite (KMD-3293) is formed via alcohol and aldehyde dehydrogenases and reaches plasma exposures similar to that of silodosin. KMD-3213G, which is not detected in animal plasma, had 1/8 times the affinity of silodosin for human α_1-AR. In animals, this human metabolite had 1/4.5 times the affinity for α_{1A}-AR subtype in rats, about ½ the inhibitory effect on contraction induced by noradrenalin in the isolated prostate in rats, and not greater than 1/10 the transferability of silodosin to the prostate. The safety pharmacology studies in which KMD-3213G was intravenously injected revealed that KMD-3213G had no meaningful effects on the central nervous system, the respiratory system, or the cardiovascular system.

Metabolite KMD-3293 was detected in animal plasma and had 1/42 times the affinity of silodosin for subtype α_{1A}-AR in humans.

TOXICOLOGY

Acute Toxicity

A single oral administration study in rats revealed that the approximate lethal dose was 800 mg/kg for males and females. The approximate lethal doses for male and female rats receiving an intravenous administration were 75 mg/kg and 90 mg/kg, respectively. The single administration study in dogs disclosed that the approximate lethal dose was 1500 mg/kg for orally administered silodosin and 50 mg/kg or more via intravenous injection.

Table 12 Single Dose Toxicity Studies in Rats and Dogs after Oral and Intravenous Administration

Species	Route	Doses (mg/kg)
Rats	oral	500, 1000, 2000
	oral	400, 800, 1600
	I.V.	0, 60, 75, 90
Dogs	oral	1500, 2000
	oral	1000, 1500
	I.V.	25, 50

Chronic Toxicity

A 1-month administration study in rats revealed fatty degeneration in liver hepatocytes given 60 mg/kg/day or more, and the no observed adverse effect level (NOAEL) of silodosin was estimated at 20 mg/kg/day. A 3-month repeat oral administration study in rats revealed moderate to severe fatty degeneration of hepatocytes and hypertrophy and eosinophilic changes of centrilobular hepatocytes in the males receiving 100 mg/kg/day or more, and hypertrophy of centrilobular hepatocytes in females receiving 400 mg/kg/day or more. The NOAEL of silodosin was estimated to be 25 mg/kg/day in males and 100 mg/kg/day in females. A 26-week oral administration study in rats showed fatty degeneration of hepatocytes in males receiving 15 mg/kg/day or more and in females given 300 mg/kg/day. Males receiving 5 mg/kg/day showed only a mild fatty degeneration of hepatocytes, which was also seen in the control group. The NOAEL of silodosin was estimated to be 5 mg/kg/day. In a 2-week intravenous injection study in rats, mortality was noted in the 50 mg/kg/day group, and the NOAEL of silodosin was estimated to be 10 mg/kg/day.

Following a 28-day administration in rats, plasma evaluations revealed decreased throxine (T4) levels at all dosage levels (50-300 mg/kg/day), increased thyroid stimulating hormone (TSH) at 150 and 300 mg/kg/day, and decreased triiodothyronine (T3) at 300 mg/kg/day. Liver to body weight ratio was increased at 150 and 300 mg/kg/day, along with thyroid/parathyroid to body weight ratio in the 300 mg/kg/day group. Histopathological examination revealed centrilobular hepatocellular hypertrophy and hypertrophy of the thyroid follicular epithelium at 150 and 300 mg/kg/day. Increased hepatic microsomal T4-UDP-GT activity was observed in the 300 mg/kg/day group. Changes in the CYP-dependent enzyme activities also occurred. Most notable were the significant increases in CYP1A at all dosage levels, increases in CYP3A in the 150 and 300 mg/kg/day groups, increases in CYP2B in the 300 mg/kg/day group, and increases in lauric acid 11-hydroxylase and lauric acid 12-hydroxylase in the 150 and 300 mg/kg/day groups.

A 1-month oral administration study in dogs showed degeneration of the seminiferous tubular epithelium in animals receiving 25 mg/kg/day or more, with the NOAEL of silodosin estimated to be less than 25 mg/kg/day. A 13-week oral administration study in dogs revealed decreased body weights in both males and females in the 50 mg/kg/day group, and atrophy of the thymus and retarded maturation of the genitalia in males given 50 mg/kg/day. The NOAEL of silodosin was estimated to be 10 mg/kg/day. A 52-week oral administration study showed decreases in body weight, erythrocyte count, hemoglobin level, and hematocrit level in dogs given 80 mg/kg/day. The NOAEL of silodosin was estimated to be 20 mg/kg/day. A 2-week intravenous administration study revealed no marked changes, and the NOAEL of silodosin was estimated at 25 mg/kg/day.

Table 13 Chronic Dose Toxicity Studies in Rats and Dogs after Oral and Intravenous Administration

Species	Route	Duration of Dosing	Doses (mg/kg)
Rat	oral	28 days	0, 50, 150, 300
		1 month	0, 30, 100, 300, 800
		1 month	0, 20, 60, 200, 600
		3 months	0, 25, 100, 400
		26 weeks	0, 15, 60, 300
		26 weeks	0, 1, 5
	I.V.	2 weeks	0, 2, 10, 50
Dog	oral	2 weeks	50, 200, 500
		1 month	0, 25, 100, 400
		13 weeks	0, 10, 50, 100/200
		52 weeks	0, 5, 20, 80
	I.V.	2 weeks	0, 1, 5, 25

Mutagenicity Studies

The reverse mutation assay in bacteria, the mouse lymphoma assay, the micronucleus test in mice, and the unscheduled DNA synthesis (UDS) test with rat hepatocytes revealed no genotoxicity potential for silodosin. A positive response was noted in the *in vitro* chromosomal aberration assay with Chinese hamster culture cells. This positive response was noted only at high levels in which cytotoxicity was noted. Silodosin did not induce chromosome aberrations in the *in vivo* genotoxicity study conducted when animals were exposed to the drug. Silodosin and its metabolites are not considered genotoxic.

Carcinogenicity Studies

In a 2-year carcinogenicity study, male mice were administered silodosin at 20, 60, and 100/200 mg/kg/day and female mice were administered 60, 150, and 400 mg/kg/day. Decreased body weights were observed at 200 mg/kg/day in males; therefore, the highest dosage was decreased to 100 mg/kg/day at Week 27 of administration. Mammary tumors and pituitary adenomas were observed in females treated at 150 mg/kg/day or higher and females treated at 400 mg/kg/day, respectively. The finding of pituitary adenomas was not statistically significant relative to controls in this study.

In a separate study conducted to elucidate the mechanism of onset of these increases in tumors, mice were administered oral doses of silodosin. Results confirmed increases in blood prolactin levels in the females receiving a single administration of 60 mg/kg/day or more and in females receiving repeat administration of 200 mg/kg/day or more. The mechanism of induction of pituitary and mammary tumors in rodents has been documented in publications as being due to the long-term, excessive stimulation by increased prolactin production and secretion from the pituitary, resulting from suppression of dopamine in the hypothalamus.[(2)] Accordingly, increased mammary gland and pituitary tumors were considered to be induced by the same mechanism as described above. Non-neoplastic lesions such as an increase in hyperplasia of mammary glands in mice receiving 150 mg/kg/day or more, hyperplasia and hypertrophy of the anterior pituitary, and increases in acinus of the breast and enlarged mammary ducts in mice given 400 mg/kg/day may also be induced by increased production of prolactin and excessive stimulation to the mammary glands. Since prolactin, as well as estrogen and progesterone, accelerates adenomyosis of the uterus in mice,[(3)] the increase in adenomyosis of the uterus in the female mice receiving 60 mg/kg/day or more may also be induced by increased blood prolactin levels.

In addition, since prolactin stimulates corpus luteal function and increases the synthesis of progesterone as described above, increases in cystic uterine glands in the uterus of mice receiving 150 mg/kg/day or more and enlargement of uterine glands in mice given 400 mg/kg/day, may result from the increased secretion of the uterine gland caused by increased progesterone. It is believed that epidemiologic examination in humans revealed that a risk of mammary gland tumors increases with increased blood prolactin in women.[(4)]

Increases in mammary gland and pituitary tumors in mice are not considered to be significant for the safety of silodosin in humans for the following reasons: repeated doses in mice of 60 mg/kg did not produce an increase in mammary tumors, and doses of 20 mg/kg did not produce an increase in prolactin levels in the blood. The 150 mg/kg/day dose is 125-fold greater, or more, on a mg/kg/day basis, than the recommended human clinical dose. Increases in prolactin levels have also been reported to be increased by AR blockers for dopamine and include the AR blockers tamsulosin and prazosin. Therefore, these data indicate that silodosin caused a significant increase in mammary tumors at 150 and 400 mg/kg via an indirect or secondary mechanism involving increases in prolactin levels that also produced non-significant increases in pituitary and hepatocellular adenomas. Tamsulosin, likewise, has induced significant increases in mammary tumors via a secondary mechanism involving hyperprolactinemia.[5] The mammary tumors noted are likely a class effect, for which there is no evidence of clinical relevance.

In the rat carcinogenicity study in which males were administered silodosin at 15, 50, and 150 mg/kg/day, and female rats received 15, 80, and 250 mg/kg/day; follicular cell adenomas of the thyroid were seen only in males of the 150 mg/kg/day group.

A repeat oral administration study in rats conducted to elucidate the possible mechanism of onset of increases in thyroid tumors revealed an increase in the liver UDP-GT activity in males receiving 150 mg/kg/day or more. A similar increase was noted in phenobarbital treated male rats. UDP-GT is involved in the metabolism and excretion of thyroid hormones. An increased UDP-GT activity enhances the catabolism of the thyroid hormones T3 and T4. The catabolism accelerates the secretion of TSH from the pituitary through an inhibition of the negative feedback mechanism. It is also known that since thyroid hormone binding protein is decreased due to catabolism, increases in unbound and free thyroid hormone occur in rats. Thus, the half-life of thyroid hormones is much shorter in rats compared to that of other species including humans.[6,7] Accordingly, the increased catabolism of thyroid hormones quickly decreases thyroid hormone levels in the blood, and the secretion of TSH is consequently increased. Thyroid tumor induction by this indirect mechanism occurs in rats more frequently than in mice, and in males more frequently than in females.[6,7] In contrast, it has been reported that thyroid tumors are not induced by this mechanism in humans.[6,7] Therefore, the neoplastic changes in the thyroid observed in the rat carcinogenicity study are considered secondary to a rat-specific, indirect mechanism, and therefore do not pose a risk to humans for the following reasons: the neoplastic changes in the thyroid are induced by the change in the catabolism of thyroid hormones by the indirect mechanism of thyroid tumor induction as previously described,[8] and there is a sufficient safety margin (72-fold) in dosage between the recommended clinical dose and 50 mg/kg/day in which follicular cell adenomas in the thyroid were not induced in male rats. Other drugs and chemicals have induced thyroid tumors in rats by a similar mechanism [9,10] and have been approved for use.

Reproduction and Teratogenicity Studies

In a study of fertility and early embryonic development and implantation in rats, it was determined that the fertility index decreased due to changes in males, and the mating index decreased due to changes in females. The NOAEL was 6 mg/kg/day for the general toxicity in males and females and 6 mg/kg/day and 20 mg/kg/day for the reproductive function and early embryonic development in males and females, respectively. No teratogenic effects were noted in either rats or rabbits in the study. The NOAEL of silodosin for reproductive function and embryo-fetal development was 1000 mg/kg/day in rats and 60 mg/kg/day in rabbits. In a study for effects on pre- and post-natal development, including maternal function in rats, the NOAEL of silodosin was 30 mg/kg/day for maternal function and 300 mg/kg/day for offspring (F_1).

Other Toxicology Studies

In a local irritation study conducted using silodosin injections (0.2 mg/mL, pH 7.15) which were to be used in the clinical pharmacology study (BA / effect of diets), no significant muscle damage in rabbits and no human blood hemolysis were observed.

An antigenicity study confirmed that silodosin demonstrated no antigenic potential in mice or guinea pigs.

An *in vitro* phototoxicity study showed that silodosin produced mild phototoxicity when exposed to Balb/c 3T3 fibroblast cells *in vitro*. Treatment with silodosin resulted in a decrease in cell survival in the presence of UV-A light, which was illustrated by a decreased uptake of neutral red. An *in vivo* phototoxicity study exposing Crl:SKH1-*hr* hairless mice to UVR radiation from a xenon lamp after a single dose of silodosin was conducted. At the highest dosages of 500 mg/kg in male mice and 400 mg/kg in female mice, the mice exhibited mild, transient erythema indicative of phototoxicity. At lower dosages of 0 (Vehicle), 20, and 100 mg/kg in male mice and 0 (Vehicle), 60, and 150 mg/kg in female mice, no skin events indicative of phototoxicity were noted. The NOAEL in male mice was 100 mg/kg and the NOAEL in female mice was 150 mg/kg, which are much greater than the human clinical dose of 0.11 mg/kg.

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PART III: CONSUMER INFORMATION

Pr pms-SILODOSIN
Silodosin Capsules

This leaflet is part III of a three-part "Product Monograph" published when pms-SILODOSIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-SILODOSIN. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this leaflet before you start taking pms-SILODOSIN (silodosin). Also, read it each time you renew your prescription, just in case new information has been added.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed pms-SILODOSIN because you have a medical condition called benign prostatic hyperplasia (BPH). This only occurs in men.

What it does:
pms-SILODOSIN relaxes muscles in the prostate, bladder neck and base. This results in improved urine flow, and reduced BPH symptoms.

When it should not be used:
Do not use pms-SILODOSIN if you:

- are allergic to silodosin or to any ingredient in pms-SILODOSIN (see **What the nonmedicinal ingredients are**);
- take other alpha1-blockers for high blood pressure;
- take antifungal or HIV drugs such as ketoconazole, itraconazole (Sporanox®), ritonavir (Kaletra®, Norvir®);
- have severe liver problem; or
- have severe kidney problem.

What the medicinal ingredient is: Silodosin

What the nonmedicinal ingredients are:
Butylhydroxytoluene, Magnesium Aluminometasilicate, Magnesium Stearate, Mannitol, Pregelatinized Starch, Polysorbate 80. Capsules contain: Gelatin and Titanium Dioxide. The markings on the capsules are in black ink, which contains Shellac, Black Iron Oxide, Propylene Glycol, Potassium Hydroxide and Water.

What dosage forms it comes in:
4 mg capsules: 4 mg of silodosin.
8 mg capsules: 8 mg of silodosin.

WARNINGS AND PRECAUTIONS

pms-SILODOSIN may lower blood pressure (postural hypotension), and may make you feel dizzy, especially when getting up from a lying or sitting position particularly if you are taking medications to lower blood pressure or have low blood pressure. In such cases, lie down until the symptoms have completely disappeared. Do not drive or operate machinery until you know how pms-SILODOSIN affects you.

pms-SILODOSIN is not indicated nor recommended for use in women and children.

Prostate cancer and BPH cause many of the same symptoms. Prior to starting pms-SILODOSIN, your doctor will examine you to rule out the presence of prostate cancer.

Tell your doctor or pharmacist, before using the medication, if:

- you suffer liver or kidneys problems;
- you have ever had a reaction to the ingredients of this medication; or
- you have had low blood pressure or signs of low blood pressure [fainting, dizziness] after taking another medicine.

If you will have eye surgery, you must inform your eye surgeon that you are currently using pms-SILODOSIN. Intraoperative Floppy Iris Syndrome (IFIS) has been reported during cataract surgery in some patients who take or have taken alpha1-blockers.

INTERACTIONS WITH THIS MEDICATION

pms-SILODOSIN is broken down by specific enzymes in the liver. It is not known how combined use of drugs, or herbal products that are also broken down by the same enzymes, or grapefruit juice may influence the effectiveness or unwanted side effects of these drugs or herbal medicines.

Before using any prescription, over-the-counter medicines or herbal products, check with your doctor or your pharmacist.

Drugs that interact with pms-SILODOSIN include:

- Alpha1-blockers for high blood pressure or prostate problems
- Certain anti-infection drugs such as ketoconazole, clarithromycin, itraconazole (Sporanox®) and ritonavir (Kaletra®, Norvir®)

PROPER USE OF THIS MEDICATION

Usual dose:

Follow your doctor's instructions very carefully about how to take pms-SILODOSIN.

The recommended dosage is one capsule (8 mg) daily to be taken right after a meal, at the same time each day.

For those with moderate renal impairment, the recommended dosage is one capsule (4 mg) daily to be taken right after meal, at the same time each day.

If you stop taking pms-SILODOSIN for several days, you must check with your doctor before starting it again.

Overdose:

Overdose of silodosin may lead to low blood pressure and change in heart rate.

If you think you have taken too much pms-SILODOSIN, contact your healthcare professional, hospital emergency department or regional poison control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all prescription drugs, pms-SILODOSIN may cause side effects.

The most common side effect seen with pms-SILODOSIN is an orgasm with reduced or no semen. This side effect is reversible with discontinuation of the product. Other common side effects include dizziness, diarrhea, lightheadedness upon standing or sitting up abruptly, headache, swelling of the throat and nasal passages, and stuffy nose. Cases of itching, hives, shortness of breath, eosinophilic pneumonia (cough, fever, difficulty breathing), dry cough, swelling under the skin, peeling of skin, redness of skin, and swelling of the face have also been reported. If these side effects persist or become bothersome, please check with your physician or pharmacist.

As with other alpha-blockers, pms-SILODOSIN can cause a drop-in blood pressure upon changing from a sitting to a standing position, especially when you start treatment. This may lead to fainting, dizziness, or lightheadedness, upon standing or sitting up abruptly. Be careful when driving, operating machinery, or when doing any dangerous activities until you know how pms-SILODOSIN affects you. This is important if you already have a problem with low blood pressure or take medicines to treat high blood pressure. If you begin to feel dizzy or lightheaded, lie down with your legs and feet up. If your symptoms do not improve call your doctor.

If you are undergoing cataract surgery or surgery because of cloudiness in your lens you should inform your ophthalmologist that you are taking pms-SILODOSIN.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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	
Common	Dizziness	✓		
	Headache	✓		
Uncommon	Fainting		✓	
	Lightheadedness upon standing or sitting up abruptly		✓	
	Liver disease or liver problems		✓	
	Allergic reactions (swollen tongue, swollen throat)			✓
	Skin rash			✓
	Red or purple discoloration of the skin caused by bleeding underneath the skin (known as purpura)	✓		
	Fast heart rate (tachycardia)		✓	
Rare	Feeling of rapid beating of		✓	

	the heart that may be more forceful (palpitat-ion)			

This is not a complete list of side effects. For any unexpected effects while taking pms-SILODOSIN, contact your doctor or pharmacist.

HOW TO STORE IT

pms-SILODOSIN capsules should be stored at controlled room temperature (15°C to 30°C). Protect from light and moisture. Keep pms-SILODOSIN out of reach and sight of children.

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.

MORE INFORMATION

If you want more information about pms-SILODOSIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Heath Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

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