For the use of Urologist only.

Silodosin Capsules

Silofast

COMPOSITION

SILOFAST-4 Capsules

Each hard gelatin capsule contains:

Silodosin ..... 4 mg

Approved colour used in empty capsule shell.

SILOFAST-8 Capsules

Each hard gelatin capsule contains:

Silodosin ..... 8 mg

Approved colour used in empty capsule shell.

DOSAGE FORM

Capsule

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Silodosin is a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors, which are located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Blockade of these alpha$_1$-adrenoreceptors can cause smooth muscle in these tissues to relax, resulting in an improvement in urine flow and a reduction in BPH symptoms.

An *in vitro* study examining the 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.

Orthostatic Effects

A test for postural hypotension was conducted 2 to 6 hours after the first dose in 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 mm Hg decrease in systolic blood pressure, or a >20 mm Hg decrease in diastolic blood pressure, or a >20 bpm increase in heart rate

Table 1: Summary of Orthostatic Test Results in 12-week, Placebo-Controlled Clinical Trials

Time of Measurement	Test Result	Silodosin N=466 n (%)	Placebo N=457 n (%)
1 minute after standing	Negative Positive	459 (98.7) 6 (1.3)	454 (99.6) 2 (0.4)
3 minutes after standing	Negative Positive	456 (98.1) 9 (1.9)	454 (99.6) 2 (0.4)

Cardiac Electrophysiology

The effect of silodosin on QT interval was evaluated in a double-blind, randomized, active-(moxifloxacin) and placebo-controlled, parallel-group study in 189 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 cytochrome (CY) P3A4 inhibitors)

QT interval was measured during a 24-hour period following dosing on day 5 (at silodosin steady state).

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 with silodosin outside the United States.

Pharmacokinetics

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 2 presents the steady state pharmacokinetics of this study.

Table 2: Mean (±SD) Steady-State Pharmacokinetic Parameters in Healthy Males Following Silodosin 8 mg Once Daily with Food

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

The absolute bioavailability is approximately 32%.

Food Effect: The maximum effect of food (i.e. co-administration with a high-fat, high-calorie meal) on the pharmacokinetics of silodosin was not evaluated. The effect of a moderate-fat, moderate-calorie meal was variable and decreased silodosin C_{max} by approximately 18 to 43% and exposure AUC by 4 to 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 the 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 four 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 the urine and 54.9% in the faeces. After intravenous administration, the plasma clearance of silodosin was approximately 10 L/hour.

Pharmacokinetics in Special Populations

Race: No clinical studies specifically investigating the effects of race have been performed.

Geriatric: In a study comparing 12 geriatric males (mean age, 69 years) and 9 young males (mean age, 24 years), the exposure (AUC) and elimination half-life of silodosin were approximately 15% and 20%, respectively, greater in geriatric than young subjects. No difference in the C_{max} of silodosin was observed

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

Renal Impairment: In a study with 6 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 with 7 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 with the normal controls.

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

Hepatic Impairment: In a study comparing 9 male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), with 9 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 has not been studied.

INDICATIONS

SILOFAST, a selective alpha$_1$-adrenergic receptor antagonist, is indicated for the treatment of the signs and symptoms of BPH.

SILOFAST capsules are not indicated for the treatment of hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is 8 mg, which is to be taken orally once daily with a meal.

Special Populations

Renal Impairment

Silodosin is contraindicated in patients with severe renal impairment (CCr <30 mL/min). In patients with moderate renal impairment (CCr: 30 to 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 to 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

CONTRAINDICATIONS

- Severe renal impairment (creatinine clearance [CCr] <30 mL/min).
- Severe hepatic impairment (Child-Pugh score ≥10).
- Concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir).
- Patients with a history of hypersensitivity to silodosin or any of the ingredients of **SILOFAST**

WARNINGS AND PRECAUTIONS

General

Orthostatic Effects

Postural 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.

Carcinoma of the prostate

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

Intraoperative Floppy Iris Syndrome

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 pre-operative dilation with standard mydriatic drugs; and potential prolapse of the iris toward the phacoemulsification incisions. Patients planning cataract surgery should be advised to inform their ophthalmologist that they are taking silodosin.

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 the prostate-specific antigen (PSA).

Drug Interactions

Moderate and Strong CYP3A4 Inhibitors

Two clinical drug interaction studies were conducted in which a single oral dose of silodosin was co-administered with the strong CYP3A4 inhibitor, ketoconazole, at doses of 400 mg and 200 mg, respectively, once daily for 4 days. Co-administration of 8 mg silodosin with 400 mg ketoconazole led to a 3.8-fold increase in the silodosin C_{max} and a 3.2-fold increase in the AUC. Co-administration of 4 mg silodosin with 200 mg ketoconazole led to similar increases: 3.7- and 2.9-fold in the silodosin C_{max} and AUC, respectively. Use of strong CYP3A4 inhibitors such as itraconazole or ritonavir may cause plasma concentrations of silodosin to increase. Concomitant administration of strong CYP3A4 inhibitors and silodosin is contraindicated.

The effect of moderate CYP3A4 inhibitors on the pharmacokinetics of silodosin has not been evaluated. Concomitant administration with moderate CYP3A4 inhibitors (e.g. diltiazem, erythromycin, verapamil) may increase the concentration of silodosin. Exercise caution and monitor patients for adverse events when co-administering silodosin with moderate CYP3A4 inhibitors particularly those that also inhibit P-glycoprotein (e.g. verapamil, erythromycin).

Strong P-glycoprotein (P-gp) Inhibitors

In vitro studies indicated that silodosin is a P-gp substrate. A drug interaction study with a strong P-gp inhibitor has not been conducted. However, in drug interaction studies with ketoconazole, a CYP3A4 inhibitor that also inhibits P-gp, significant increase in exposure to silodosin was observed. Inhibition of P-gp may lead to increased silodosin concentration. Silodosin is not recommended in patients taking strong P-gp inhibitors such as cyclosporine.

Digoxin

The effect of silodosin on the pharmacokinetics of digoxin was evaluated in a multiple dose, single-sequence, crossover study of 16 healthy males, aged 18 to 45 years. A loading dose of digoxin was administered as 0.5 mg twice daily for one day. Following the loading doses, digoxin (0.25 mg once daily) was administered alone for 7 days and then concomitantly with silodosin 4 mg twice a day for the next 7 days. No significant differences in digoxin AUC and C_{max} were observed when digoxin was administered alone or concomitantly with silodosin. No dose adjustment is required.

Alpha-Blockers

The pharmacodynamic interactions between silodosin and other alpha-blockers have not been determined. However, interactions may be expected and silodosin should not be used in combination with other alpha-blockers.

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. Co-administration of silodosin with a single dose of 100 mg sildenafil or 20 mg tadalafil was evaluated in a placebo-controlled clinical study that included 24 healthy male subjects, 45 to 78 years of age. Orthostatic vital signs were monitored in the 12-hour period following concomitant dosing. During this period, the total number of positive orthostatic test results was greater in the group receiving silodosin plus a PDE5 inhibitor compared with silodosin alone. No events of symptomatic orthostasis or dizziness were reported in subjects receiving silodosin with a PDE5 inhibitor. Caution is advised when alpha-adrenergic blocking agents, including silodosin, are co-administered with PDE5 inhibitors.

Other Concomitant Drug Therapy

Antihypertensives

The pharmacodynamic interactions between silodosin and antihypertensives have not been rigorously investigated in a clinical study. However, approximately one-third of the patients in clinical studies used concomitant antihypertensive medications with silodosin. 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). Caution should be exercised during concomitant use with antihypertensives and patients should be monitored for possible adverse events.

Metabolic Interactions

In vitro studies indicated that silodosin administration is not likely to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 or induce the activity of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and P-gp.

Information for Patients

Patients should be instructed to take silodosin once daily with a meal.

Patients should be instructed about the possible occurrence of symptoms related to postural hypotension (such as dizziness), and should be cautioned about driving, operating machinery, or performing hazardous tasks until they know how silodosin will affect them. This is especially important for those with low blood pressure or who are taking antihypertensive medications.

The most common side effect seen with silodosin is an orgasm with reduced or no semen. This side effect does not pose a safety concern and is reversible with discontinuation of the product.

The patient should be instructed to tell his ophthalmologist about the use of silodosin before cataract surgery or other procedures involving the eyes, even if the patient is no longer taking silodosin.

Renal Impairment

The effect of renal impairment on silodosin pharmacokinetics was evaluated in a single dose study of six male patients with moderate renal impairment and seven male subjects with normal renal function. Plasma concentrations of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function.

Silodosin should be reduced to 4 mg per day in patients with moderate renal impairment. Exercise caution and monitor patients for adverse events.

Silodosin has not been studied in patients with severe renal impairment. Silodosin is contraindicated in patients with severe renal impairment.

Hepatic Impairment

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 pharmacokinetics of silodosin were not significantly altered in patients with hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment.

Silodosin has not been studied in patients with severe hepatic impairment. Silodosin is contraindicated in patients with severe hepatic impairment

Pregnancy

Pregnancy Category B

Silodosin is not indicated for use in women.

Lactation

Silodosin capsules are not indicated for use in women

Paediatric Use

Silodosin is not indicated for use in paediatric patients. Safety and effectiveness in paediatric patients have not been established.

Geriatric Use

In double-blind, placebo-controlled, 12-week clinical studies of silodosin, 259 (55.6%) patients were below 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 less than 65 years of age (1.2% for placebo), 2.9% of silodosin patients 65 years of age and over (1.9% for placebo), and 5.0% of patients 75 years of age and over (0% for placebo). There were otherwise no significant differences in safety or effectiveness between older and younger patients.

UNDESIRABLE EFFECTS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug can not be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In U.S. 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.

In double-blind, placebo-controlled, 12-week clinical trials, 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). The majority (72.1%) of adverse reactions for the silodosin-treated patients (59.8% for placebo-treated) were qualified by the investigator as mild. 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.

Adverse Reactions Observed in At Least 2% of Patients

The incidence of treatment-emergent adverse reactions listed in the following table were derived from two 12-week, multicentre, double-blind, placebo-controlled clinical studies of silodosin 8 mg daily in BPH patients. Adverse reactions that occurred in at least 2% of patients treated with silodosin and more frequently than with placebo are shown in Table 3

Table 3: Adverse Reactions Occurring in ≥2% of Patients in 12-week, Placebo-Controlled Clinical Trials

Adverse Reactions	Silodosin N=466 n (%) n (%)	Placebo N=457 n (%)
Retrograde ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhoea	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 the above clinical trials, the following adverse events were also reported by between 1% and 2% of patients receiving silodosin and occurred more frequently than with placebo: insomnia, PSA increased, sinusitis, abdominal pain, asthenia and rhinorrhoea. One case of syncope in a patient taking prazosin concomitantly and one case of priapism were reported in the silodosin treatment group.

In a 9-month open-label safety study of silodosin, one case of intraoperative floppy iris syndrome was reported.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of silodosin. Because these reactions 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:

Skin and Subcutaneous Tissue Disorders: Toxic skin eruption, purpura, skin rash, pruritus and urticarial.

Hepatobiliary Disorders: Jaundice, impaired hepatic function associated with increased transaminase values.

Immune System Disorders: Allergic-type reactions, not limited to skin reactions, including swollen tongue and pharyngeal oedema, resulting in serious outcomes.

If you experience any side effects, talk to your doctor or pharmacist or write to **drugsafety@cipla.com.** You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024.**

By reporting side effects, you can help provide more information on the safety of this product.

OVERDOSAGE

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

STORAGE AND HANDLING INSTRUCTIONS

Store below 30°C, Protect from light and moisture.

PACKAGING INFORMATION

SILOFAST-4: Blister pack of 15 capsules
SILOFAST-8: Blister pack of 15 capsules

Last updated: August 2015
Last reviewed: April 2017

B31094-01

Cipla

99317009