For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

SILOXIO 4/ SILOXIO 8

1. Generic Name

Silodosin Capsules 4 mg and 8 mg.

2. Qualitative and quantitative Composition:

Each Hard Gelatin Capsule Contains:

Silodosin JP…….…. 4 mg/8 mg.

Excipients……. q.s.

Colours: Approved colours used in empty capsules shells.

The excipients used are Colloidal Silicon Dioxide, Isopropyl Alcohol, Magnesium Stearate, Mannitol, Povidone, Sodium Lauryl Sulphate, Sodium Starch Glycolate.

3. Dosage form and strength

Dosage form: Hard Gelatin Capsule

Strength: Silodosin 4 mg and 8 mg

4. Clinical particulars

4.1. Therapeutic indication

For the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) in adults only.

4.2. Posology and method of administration

Posology

The recommended dosage is 1 capsule once daily or as directed by the Physician.

Method of administration

For oral administration only.

4.3. Contraindications

Silodosin is contraindicated for use in the following:

- Severe renal impairment (CCr <30 mL/min).
- Concomitant administration with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir)

4.4. Special warnings and precautions for use

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.

Renal Impairment

In a clinical pharmacology study, plasma concentrations (AUC and C_{max}) of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function, while half-lives of silodosin doubled in duration. The dose

of silodosin should be reduced to 4 mg in patients with moderate renal impairment. Exercise caution and monitor such patients for adverse events. Silodosin is contraindicated in patients with severe renal impairment.

Hepatic Impairment

Silodosin has not been tested in patients with severe hepatic impairment, and therefore, should not be prescribed to such patients.

Pharmacokinetic Drug-Drug Interactions

In a drug interaction study, co-administration of a single 8 mg dose of silodosin with 400 mg ketoconazole, a strong CYP3A4 inhibitor, caused a 3.8-fold increase in maximum plasma silodosin concentrations and 3.2-fold increase in silodosin exposure (i.e., AUC). Concomitant use of ketoconazole or other strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir) is therefore contraindicated.

Pharmacodynamic Drug-Drug Interactions

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. A specific pharmacodynamic interaction study between silodosin and antihypertensive agents has not been performed. However, patients in the Phase 3 clinical studies taking concomitant antihypertensive medications with silodosin did not experience a significant increase in the incidence of syncope, dizziness, or orthostasis. Nevertheless, exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events.

Caution is also advised when alpha-adrenergic blocking agents including silodosin 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.

Carcinoma of the Prostate

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 silodosin 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 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 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 prostate-specific antigen (PSA).

4.5. Drugs interactions

Moderate and Strong CYP3A4 Inhibitors

In a clinical metabolic inhibition study, a 3.8-fold increase in silodosin maximum plasma concentrations and 3.2-fold increase in silodosin exposure were observed with concurrent

administration of a strong CYP3A4 inhibitor, 400 mg ketoconazole. 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 concentration of silodosin. Exercise caution and monitor patients for adverse events when co-administering silodosin with moderate CYP3A4 inhibitors.

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. silodosin is therefore not recommended in patients taking strong P-gp inhibitors such as cyclosporine.

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.

Digoxin

The effect of co-administration of silodosin and digoxin 0.25 mg/day for 7 days was evaluated in a clinical trial in 16 healthy males, aged 18 to 45 years. Concomitant administration of silodosin and digoxin did not significantly alter the steady state pharmacokinetics of digoxin. No dose adjustment is required.

PDE5 Inhibitors

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.

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). Exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events.

Metabolic Interactions: In *vitro* data indicate that silodosin does not have the potential to inhibit or induce cytochrome P450 enzyme systems.

Food Interactions

The effect of a moderate fat, moderate calorie meal on silodosin pharmacokinetics was variable and decreased silodosin maximum plasma concentration (C_{max}) by approximately 18% to 43% and exposure (AUC) by 4% to 49% across three different studies. Safety and efficacy clinical

trials for silodosin were always conducted in the presence of food intake. Patients should be instructed to take silodosin with a meal to reduce risk of adverse events.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Pregnancy Category B. Silodosin is not indicated for use in women.

An embryo/fetal study in rabbits showed decreased maternal body weight at 200 mg/kg/day (approximately 13 to 25 times the maximum recommended human exposure or MRHE of silodosin via AUC). No statistically significant teratogenicity was observed at this dose.

Silodosin was not teratogenic when administered to pregnant rats during organogenesis at 1000 mg/kg/day (estimated to be approximately 20 times the MRHE). No maternal or fetal effects were observed at this dose. Rats and rabbits do not produce glucuronidated silodosin, which is present in human serum at approximately 4 times the level of circulating silodosin and which has similar pharmacological activity to silodosin.

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No effects on physical or behavioral development of offspring were observed when rats were treated during pregnancy and lactation at up to 300 mg/kg/day.

Lactation

Silodosin tablets are not indicated for use in women.

Pediatric Use

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

Geriatric Use

In double-blind, placebo-controlled, 12-week clinical studies of silodosin, 259 (55.6%) 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.

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.

4.7. Effects on ability to drive and use machines

No studies on the effects of Silodosin on the ability to drive and use machines have been performed. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Silodosin.

4.8. 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 cannot 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.

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

Adverse Reactions	**Silodosin N=466 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 urticaria.

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 edema resulting in serious outcomes.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

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.

5. Pharmacological properties

5.1. 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 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.

5.2. Pharmacodynamic properties

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.

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.

5.3. Pharmacokinetic properties

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

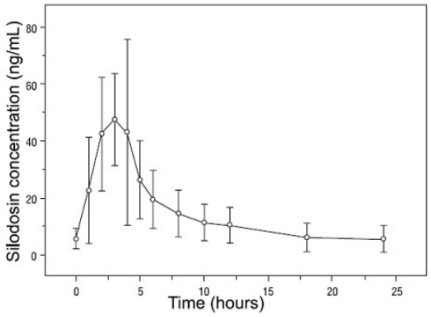
The pharmacokinetic characteristics of silodosin 8 mg once daily were determined in a multi-dose, open-label, 7-day pharmacokinetic study completed in 19 healthy, target-aged (greater than or equal to 45 years of age) male subjects. Table presents the steady state pharmacokinetics of this study.

Table 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.

Figure 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%.

Food Effect

The maximum effect of food (i.e., co-administration with a high fat, high calorie meal) on the PK of silodosin was not evaluated. The effect of a moderate fat, moderate calorie meal was variable and decreased silodosin Cmax by approximately 18% - 43% and AUC by 4% - 49% across three different studies.

In a single-center, open-label, single-dose, randomized, two-period crossover study in twenty healthy male subjects age 21 to 43 years under fed conditions, a study was conducted to evaluate the relative bioavailability of the contents of an 8 mg capsule of silodosin sprinkled on applesauce compared to the product administered as an intact capsule. Based on AUC_{0-24} and C_{max} , silodosin administered by sprinkling the contents of a silodosin capsule onto a tablespoonful of applesauce was found to be bioequivalent to administering the capsule whole.

Distribution

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

Elimination

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). Coadministration 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 urine and 54.9% in feces. After intravenous administration, the plasma clearance of silodosin was approximately 10 L/hour.

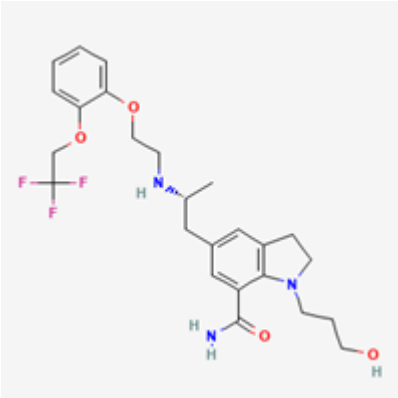
6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

The toxicity profile of silodosin, a selective alpha (1A)-adrenoceptor antagonist, was evaluated. The lethal doses were 800 mg/kg in rats and 1500 mg/kg in dogs. Repeated-dose studies revealed fatty degeneration of hepatocytes and an induction of drug-metabolizing enzymes at 15 mg/kg/day or more in male rats, mammary gland hyperplasia at 60 mg/kg/day or more in female rats, and degeneration of the seminiferous tubular epithelium at 25 mg/kg/day or more only in young dogs.

7. Description

Silodosin is 1-(3-hydroxypropyl)-5-[(2R)-2-[2-[2-(2,2,2 trifluoroethoxy) phenoxy]ethylamino] propyl]-2,3-dihydroindole-7-carboxamide The empiric formula of $C_{25}H_{32}F_3N_3O_4$ and its molecular weight is 495.5 g/mol. Its structural formula is:



SILOXIO 4

SILOXIO 4 is Brown cap and white body hard gelatin capsules size “3” containing white to off white colored granules powder.

SILOXIO 8

SILOXIO 8 is Dark Blue cap and white body size “1” hard gelatin capsules containing white to off white colored granules powder.

The excipients used are Colloidal Silicon Dioxide, Isopropyl Alcohol, Magnesium Stearate, Mannitol, Povidone, Sodium Lauryl Sulphate, Sodium Starch Glycolate.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

SILOXIO is packed in 10 Capsules.

8.4. Storage and handing instructions

Store protected from light & Moisture at a temperature not exceeding 30°C.

Keep all medicine out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Pure & Cure Healthcare Pvt. Ltd.

Plot No.-26A, 27-30, Sector-8A,

I.I.E., SIDCUL, Ranipur,

Haridwar-249 403, Uttarakhand, India.

11. Details of permission or licence number with date

Mfg Lic No. 31/UA/2013 issued on 02.01.2024.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/SILOXIO 4 mg/8mg/SEP-2025/01/PI