SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Silodosin capsules

URYDOS

Strength:

4mg

Pharmaceutical form

Capsules for oral administration

Prescription only Medicine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Silodosin .....4 mg

3. PHARMACEUTICAL FORM

Capsules

Silodosin 4 mg

Size '3', hard gelatin capsules, cap imprinted with "ML" in gold ink and body imprinted with "4 mg" in gold ink filled with white to off white powder.

Blister pack of 10's

4. CLINICAL PARTICULARS

4.1.Therapeutic indications

Silodosin, a selective alpha-1 adrenergic receptor antagonist, is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Silodosin is not indicated for the treatment of hypertension.

4.2.Posology and method of administration

The recommended dose is 8 mg orally once daily with a meal. .

Capsules should not be broken or chewed, it should be swallowed whole with sufficient water.

Dosage Adjustment in Special Populations

Renal impairment: SILODOSIN is contraindicated in patients with severe renal impairment (CCr < 30 mL/min). In patients with moderate renal impairment (CCr 30-50 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

4.3 Contraindications

- Severe renal impairment (CCr < 30 mL/min)
- Severe hepatic impairment (Child-Pugh score > 10)
- Concomitant administration with strong Cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir)
- Patients with a history of hypersensitivity to Silodosin or any of the ingredients of Silodosin

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 Cmax) 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

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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

DE5 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

Antihypertensive

The Pharmacodynamic interactions between silodosin and antihypertensive 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 antihypertensive 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 (Cmax) 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 Pregnancy and lactation

Not applicable as silodosin is intended for male patients only.

4.7 Effects on ability to drive and use machines

Silodosin has minor or moderate influence on the ability to drive and use machines. Patients should be informed about the possible occurrence of symptoms related to postural hypotension (such as dizziness) and should be cautioned about driving or operating machines until they know how silodosin will affect them.

4.8 Undesirable effects

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, multicenter, 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 1.

Table 1 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)
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 the two 12-week, placebo-controlled clinical trials, the following adverse events were 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 rhinorrhea. 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 (IFIS) was reported.

Post marketing 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

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.

1. PHARMACOLOGICAL PROPERTIES

1.1.Pharmacodynamic properties

Silodosin is a selective antagonist of post-synaptic alpha-1 adrenoreceptor, which are located in the human prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. Blockade of these alpha-1 adrenoreceptor 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 adrenoreceptor (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.

1.2.Pharmacokinetic properties

Absorption

Silodosin administered orally is well absorbed and absorption is dose proportional. The absolute bioavailability is approximately 32 %

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 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 14C-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

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 Cmax of silodosin was observed.

Pediatric

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

Renal Impairment

In a study with six subjects with moderate renal impairment, the total silodosin (bound and unbound) AUC, Cmax, 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 Cmax were 2.0- and 1.5-fold higher, respectively, in subjects with moderate renal impairment compared to the normal controls.

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 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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2-year oral carcinogenicity study in rats administered doses up to 150 mg/kg/day [about 8 times the exposure of the maximum recommended human dose (MRHE) based on AUC of silodosin], an increase in thyroid follicular cell tumor incidence was seen in male rats receiving doses of 150 mg/kg/day. Silodosin induced stimulation of thyroid stimulating hormone (TSH) secretion in the male rat as a result of increased metabolism and decreased circulating levels of thyroxine (T4). These changes are believed to produce specific morphological and functional changes in the rat thyroid including hypertrophy, hyperplasia, and neoplasia. Silodosin did not alter TSH or T4 levels in clinical trials and no effects based on thyroid examinations were noted. The relevance to human risk of these thyroid tumors in rats is not known.

In a 2-year oral carcinogenicity study in mice administered doses up to 100 mg/kg/day in males (about nine times the MRHE based on AUC of silodosin) and 400 mg/kg/day in females (about 72 times the MRHE based on AUC), there were no significant tumor findings in male mice. Female mice treated for 2 years with doses of 150 mg/kg/day (about 29 times the MRHE based on AUC) or greater had statistically significant increases in the incidence of mammary gland adenoacanthomas and adenocarcinomas. The increased incidence of mammary gland neoplasms in female mice was considered secondary to silodosin-induced Hyperprolactinemia measured in the treated mice. Elevated prolactin levels were not observed in clinical trials. The relevance to human risk of prolactin-mediated endocrine tumors in mice is not known. Rats and mice do not produce glucuronidated silodosin, which is present in human serum at approximately four times the level of circulating silodosin and which has similar pharmacological activity to silodosin. Silodosin produced no evidence of mutagenic or genotoxic potential in the in vitro Ames assay, mouse lymphoma assay, unscheduled DNA synthesis assay and the in vivo mouse micronucleus assay. A weakly positive response was obtained in two in vitro Chinese Hamster Lung (CHL) tests for chromosomal aberration assays at high, cytotoxic concentrations.

Treatment of male rats with silodosin for 15 days resulted in decreased fertility at the high dose of 20 mg/kg/day (about twice the MRHE) which was reversible following a two week recovery period. No effect was observed at 6 mg/kg/day. The clinical relevance of this finding is not known.

In a fertility study in female rats, the high dose of 20 mg/kg/day (about 1 to 4 times the MRHE) resulted in estrus cycle changes, but no effect on fertility. No effect on the estrus cycle was observed at 6 mg/kg/day.

In a male rat fertility study, sperm viability and count were significantly lower after administration of 600 mg/kg/day (about 65 times the MRHE) for one month. Histopathological examination of infertile males revealed changes in the testes and epididymides at 200 mg/kg/day (about 30 times the MRHE).

1. PHARMACEUTICAL PARTICULARS

1.1.List of excipients

Silodosin 4mg

Mannitol

Mannogem ®EZ Spray Dried Mannitol

Pregelatinised starch

Sodium Lauryl Sulphate

Magnesium stearate

White opaque cap, white opaque body, size '3', hard gelatin capsules, cap imprinted with "ML" in gold ink and body imprinted with "4 mg" in gold ink

1.2.Incompatibilities

Not Applicable

1.3.Shelf life

24 months

6.4 Special precautions for storage

Not applicable

6.5 Nature and contents of container

Blister pack of 10's

6.6 Special precautions for disposal and other handling

No Special requirement

7. Marketing Authorization Holder

MICRO LABS LIMITED

#31, Race course road

Bangalore-560001

INDIA

8. Marketing authorisation number.

TAN 21 HM 0429

9. Date of authorization or of the last renewal of the authorization

2021-08-20

10. Date of revision of the text