SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Siloxin (Silodosin) Capsules 8mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains
Silodosin……8mg

3. PHARMACEUTICAL FORM

Hard gelatin capsule with pink opaque cap and white opaque body, containing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Siloxin (Silodosin) is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration Recommended Dose

Siloxin (Silodosin) 8mg once daily with a meal is recommended as the dose for the treatment of the signs and symptoms of BPH.

Missed Dose

If a dose of Siloxin (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

Siloxin (Silodosin) should be taken orally once daily with a meal. Siloxin (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.

Special Population

Renal impairment

In patients with moderate renal impairment, the dose should be reduced to 4mg once daily taken with a meal. No dosage adjustment is needed in patients with mild renal impairment.

Hepatic impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment.

Geriatric
No dosage adjustment is needed in elderly patients

4.3 Contraindications

Silodosin is contraindicated:

- In patients with known hypersensitivity to silodosin or to any excipient of the product.
- In patients with severe renal impairment.
- In patients with severe hepatic impairment.
- Concomitant administration with strong Cytochrome P450 3A4
- (CYP3A4) inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir).
- Silodosin should not be administered to patients using concomitant alpha-blockers (e.g., prazosin, terazosin, doxazosin).

4.4 Special warnings and special precautions for use

- As with all alpha-1 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.
- 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 has been observed during cataract surgery in some patients on alpha-1 blockers or previously treated with alpha-1 blockers. Patients planning cataract surgery should be told to inform their ophthalmologist that they are taking silodosin.
- Treatment with silodosin leads to a decrease in the amount of semen released during orgasm that may temporarily affect male fertility. This effect disappears after discontinuation of silodosin.
- 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.
- Exercise caution and monitor patients with moderate renal impairment for adverse events.

4.5 Interaction with other medicaments and other forms of interaction

Moderate CYP3A4 Inhibitors

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

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.

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

PDE-5 Inhibitors
Patients taking PDE-5 Inhibitors concomitantly with silodosin should be monitoired for possible adverse events. Silodosin can potentially cause symptomatic hypotension

4.6 Fertility, pregnancy and lactation Pregnancy & Nursing Mothers

Silodosin is not indicated nor recommended for use in women.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Very Common
Ejaculatory disorders, including retrograde ejaculation and an ejaculation.

Common
Dizziness, orthostatic hypotension, nasal congestion and diarrhoea.
Uncommon
Libido decreased, tachycardia, hypotension, nausea, dry mouth, abnormal liver function tests, skin rash, pruritus, urtricaria, drug eruption, erectile dysfunction and Intraoperative Floppy Iris Syndrome.
Rare
Syncope, loss of consciousness and palpitations.

Very Rare
Allergic type reactions including facial swelling, swollen tongue and pharyngeal oedema.

'Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS https://pv.pharmacyboardkenya.org'

4.9 Overdose

Adverse event reported with silodosin overdose was postural hypotension.

Treatment
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 Pharmacodynamics properties

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 benign prostatic hyperplasia (BPH) symptoms.

5.2 Pharmacokinetic properties

Absorption

Silodosin administered orally is well absorbed and absorption is dose proportional. The absolute bioavailability is approximately 32%. Food decreases C_{max} by approximately 30%, increases t_{max} by approximately 1 hour and has little effect on AUC.

Distribution

Silodosin has an apparent volume of distribution of 49.5L 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). 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 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 Population

Geriatric Patients

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

Renal impairment

Exposure to silodosin (unbound) in subjects with mild and moderate renal impairment resulted, on average, in an increase of C_{max} (1.6-fold) and AUC (1.7-fold) relative to subjects with normal renal function. In subjects with severe

renal impairment increase of exposure was 2.2-fold for Cmax and 3.7-fold for AUC. Exposure to the main metabolites, silodosin glucuronide and KMD3293, was also increased.

Pediatric

Safety and effectiveness of silodosin on pediatric patients have not been established.

5.3 Preclinical safety data

In a 2-year oral carcinogenicity study in rats administered doses up to 150 mg/kg/day [about 8 times the exposure at the MRHD 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 9 times the exposure at the MRHD based on AUC of silodosin) and 400 mg/kg/day in females (about 72 times the exposure at the MRHD 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 exposure at the MRHD 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 2 times the exposure at the MRHD based on AUC) 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 exposure at the MRHD based on AUC) 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 exposure at the MRHD based on AUC) for one month. Histopathological examination of infertile

males revealed changes in the testes and epididymides at 200 mg/kg/day (about 30 times the exposure at the MRHD based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Mannitol
- Starch 1500 (Partially Pregelatinized)
- Sodium Lauryl Sulfate
- Magnesium Stearate
- Purified water
- EGC Silodosin 8mg Size "1"

6.2 Incompatibilities

None.

6.3 Shelf-life

2 years

The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

- Do not store above 30°C.
- Protect from light and moisture.
- The expiry date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

Siloxin (Silodosin) Capsules 4mg are available in Alu-Alu blister pack of 10's (1 x 10 Capsules), packed in a printed unit carton along with the package insert.

6.6 Special precautions for disposal and other handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi
74900, Pakistan Tel: (92-21) 5063100-03
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8. MARKETING AUTHORIZATION NUMBER

H2025/CTD9728/21075

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

31-03-2025

10. DATE OF REVISION OF THE TEXT

31-03-2025