Austell Pharmaceuticals (Pty) Ltd, 540107 and 540108, SILDOS 4 mg and SILDOS 8 mg, Hard gelatin capsules, 4 mg and 8 mg.

Approved Professional Information for Medicines for Human Use:

SILDOS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SILDOS 4 mg hard gelatin capsules

SILDOS 8 mg hard gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SILDOS 4 mg hard gelatin capsule

Each hard gelatin capsule contains 4 mg silodosin

SILDOS 8 mg hard gelatin capsule

Each hard gelatin capsule contains 8 mg silodosin

Contains sugar:

SILDOS 4 mg: mannitol 117 mg/capsule

SILDOS 8 mg: mannitol 234 mg/capsule

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SILDOS 4 mg: Yellow, opaque, hard gelatin capsule, size 3, printed with black ink “4” on the cap.

SILDOS 8 mg: White, opaque, hard gelatin capsule, size 0, printed with black ink "8" on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended dose is one capsule of SILDOS 8 mg daily.

For special patient populations, one capsule of SILDOS 4 mg daily is recommended (see below).

Special populations

Elderly

No dose adjustment is required in the elderly.

Renal Impairment

No dosage adjustment is required in patients with mild renal impairment (Cl_{CR} ≥ 50 to ≤ 80 mL/min).

A starting dose of 4 mg once daily is recommended in patients with moderate renal impairment (CL_{CR} ≥ 30 to < 50 mL/min), which may be increased to 8 mg once daily after one week of treatment, depending on the individual patient's response. The use in patients with severe renal impairment (CL_{CR} < 30 mL/min) is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild to moderate hepatic impairment. As no data are available, the use in patients with severe hepatic impairment is not recommended (see sections 4.4 and 5.2).

Paediatric population

There is no relevant indication for use of SILDOS in the paediatric population.

Method of administration

Oral use. The capsule should be taken with food, preferably at the same time every day. The capsule should not be broken or chewed but swallowed whole, preferably with a glass of water.

4.3 Contraindications

- Hypersensitivity to silodosin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Intraoperative Floppy Iris Syndrome (IFIS)

IFIS (a variant of small pupil syndrome) has been observed during cataract surgery in some patients on α_1-blockers or previously treated with α_1-blockers. This may lead to increased procedural complications during the operation.

The initiation of therapy with silodosin is not recommended in patients for whom cataract surgery is scheduled. Discontinuing treatment with an α_1-blocker 1-2 weeks prior to cataract surgery has been recommended, but the benefit and duration of stopping the therapy prior to cataract surgery has not yet been established.

During pre-operative assessment, eye surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with silodosin, in order to ensure that appropriate measures will be in place to manage IFIS during surgery.

Orthostatic effects

The incidence of orthostatic effects with silodosin is very low. However, a reduction in blood pressure can occur in individual patients, leading to syncope. At the first signs of orthostatic hypotension (such as postural dizziness), the patient should sit or lie down until the symptoms have disappeared. In patients with orthostatic hypotension, treatment with silodosin is not recommended.

Renal impairment

The use of SILDOS in patients with severe renal impairment (CL_{CR} < 30 mL/min) is not recommended (see sections 4.2 and 5.2).

Hepatic impairment

Since no data are available in patients with severe hepatic impairment, the use of SILDOS in these patients is not recommended (see sections 4.2 and 5.2).

Carcinoma of the prostate

Since BPH and prostate carcinoma may present the same symptoms and can co-exist, patients thought to have BPH should be examined prior to starting therapy with SILDOS, to rule out the presence of carcinoma of the prostate. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

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 (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Silodosin is metabolised extensively, mainly via CYP3A4, alcohol dehydrogenase and UGT2B7. Silodosin is also a substrate for P-glycoprotein. Substances that inhibit (such as ketoconazole, itraconazole, ritonavir or cyclosporine) or induce (such as rifampicin, barbiturates, carbamazepine, phenytoin) these enzymes and transporters may affect the plasma concentrations of silodosin and its active metabolite.

Alpha-blockers

There is inadequate information about the safe use of silodosin in association with other α-adrenoreceptor antagonists. Consequently, the concomitant use of other α-adrenoreceptor antagonists is not recommended.

CYP3A4 inhibitors

In an interaction study, a 3,7-fold increase in maximum silodosin plasma concentrations and a 3,1-fold increase in silodosin exposure (i.e. AUC) were observed with concurrent administration of a potent CYP3A4 inhibitor (ketoconazole 400 mg). Concomitant use with potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir or cyclosporine) is not recommended.

When silodosin was co-administered with a CYP3A4 inhibitor of moderate potency such as diltiazem, an increase in silodosin AUC of approximately 30 % was observed, but C_{max} and half-life were not affected. This change is clinically not relevant and no dose adjustment is required.

PDE-5 inhibitors

Minimal pharmacodynamic interactions have been observed between silodosin and maximum doses of sildenafil or tadalafil. In a placebo-controlled study in subjects 45-78 years of age receiving silodosin, the co-administration of sildenafil 100 mg or tadalafil 20 mg induced no clinically meaningful mean decreases in systolic or diastolic blood pressure, as assessed by orthostatic tests (standing *versus* supine). In the subjects over 65 years, the mean decreases at the various time points were between 5 and 15 mmHg (systolic) and 0 and 10 mmHg (diastolic). Positive orthostatic tests were only slightly more common during co-administration; however, no symptomatic orthostasis or dizziness occurred. Patients taking PDE-5 inhibitors concomitantly with silodosin should be monitored for possible adverse reactions.

Antihypertensives

In the clinical study program, many patients were on concomitant antihypertensive therapy (mostly medicines acting on the renin-angiotensin system, beta-blockers, calcium antagonists and diuretics) without experiencing an increase in the incidence of orthostatic hypotension. Nevertheless, caution should be exercised when starting concomitant use with antihypertensives and patients should be monitored for possible adverse reactions.

Digoxin

Steady state levels of digoxin, a substrate of P-glycoprotein, were not significantly affected by co-administration with silodosin 8 mg once daily. No dose adjustment is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not applicable as silodosin is intended for male patients only.

Breastfeeding

Not applicable as silodosin is intended for male patients only.

Fertility

In clinical studies, the occurrence of ejaculation with reduced or no semen has been observed during treatment with silodosin due to the pharmacodynamic properties of silodosin. Before starting treatment, the patient should be informed that this effect may occur, temporarily affecting male fertility.

4.7 Effects on ability to drive and use machines

SILDOS 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

a) Summary of the safety profile

The most frequently observed adverse reactions reported with silodosin in clinical studies and during long-term use were ejaculatory disorders such as retrograde ejaculation and anejaculation (ejaculatory volume reduced or absent). This may temporarily affect male fertility. It is reversible within a few days upon discontinuation of treatment (see section 4.4).

b) Tabulated list of adverse reactions

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Immune system disorders		Allergic type reactions include facial swelling, tongue and pharyngealoedema	
Psychiatric disorders		Libido decreased	
Nervous system disorders	Dizziness	Syncope, loss of consciousness	
Cardiac disorders		Tachycardia, Palpitations	

Vascular disorders	Orthostatic hypotension	Hypotension	
Respiratory, thoracic and mediastinal disorders	Nasal congestion		
Gastrointestinal disorders	Diarrhoea	Nausea, dry mouth	
Hepatobiliary disorders		Abnormal liver function tests	
Skin and subcutaneous tissue disorders		Skin rash, pruritus, urticaria, drug eruption	
Reproductive system and breast disorders	Ejaculatory disorders, including retrograde ejaculation, anejaculation	Erectile dysfunction	

Injury, poisoning and procedural complications			Intraoperative floppy iris syndrome

c. Description of selected adverse reactions

Orthostatic hypotension:

Orthostatic hypotension may occasionally lead to syncope (see section 4.4).

Intraoperative Floppy Iris Syndrome (IFIS):

IFIS has been reported during cataract surgery (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications:

https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Silodosin was evaluated at doses of up to 48 mg/day in healthy male subjects. The dose-limiting adverse reaction was postural hypotension. If ingestion is recent, induction of vomiting may be considered. Should overdose of silodosin lead to hypotension, cardiovascular support has to be provided. Dialysis is unlikely to be of significant benefit since silodosin is highly (96,6 %) protein bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A. 32.2 other

Pharmacotherapeutic group: Urologicals, alpha-adrenoreceptor antagonists, ATC code: G04CA04.

Mechanism of action

Silodosin is highly selective for α_{1A}-adrenoreceptors that are primarily located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Blockade of these α_{1A}-adrenoreceptors causes smooth muscle in these tissues to relax, thus decreasing bladder outlet resistance, without affecting detrusor smooth muscle contractility. This causes an improvement of both storage (irritative) and voiding (obstructive) symptoms (lower urinary tract symptoms, LUTS) associated with benign prostatic hyperplasia.

Silodosin has a substantially lower affinity for the α_{1B}-adrenoreceptors that are primarily located in the cardiovascular system. It has been demonstrated *in vitro* that the α_{1A}:α_{1B} binding ratio of silodosin (162:1) is extremely high.

5.2 Pharmacokinetic properties

The pharmacokinetics of silodosin and its main metabolites have been evaluated in adult male subjects with and without BPH after single and multiple administrations with doses ranging from 0,1 mg to 48 mg per day. The pharmacokinetics of silodosin is linear throughout this dose range.

The exposure to the main metabolite in plasma, silodosin glucuronide (KMD-3213G), at steady-state is about 3-fold that of the parent substance. Silodosin and its glucuronide reach steady-state after 3 days and 5 days of treatment, respectively.

Absorption

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

An *in vitro* study with Caco-2 cells showed that silodosin is a substrate for P-glycoprotein.

Food decreases C_{max} by approximately 30 %, increases t_{max} by approximately 1 hour and has little effect on AUC.

In healthy male subjects of the target age range (n=16, mean age 55±8 years) after once-a-day oral administration of 8 mg immediately after breakfast for 7 days, the following pharmacokinetic parameters were obtained: C_{max} 87±51 ng/ml (sd), t_{max} 2,5 hours (range 1,0 – 3,0), AUC 433±286 ng • h/mL

Distribution

Silodosin has a volume of distribution of 0,81 l/kg and is 96,6 % bound to plasma proteins. It does not distribute into blood cells.

Protein binding of silodosin glucuronide is 91 %.

Biotransformation

Silodosin undergoes extensive metabolism through glucuronidation (UGT2B7), alcohol and aldehyde dehydrogenase and oxidative pathways, mainly CYP3A4. The main metabolite in plasma, the glucuronide conjugate of silodosin (KMD-3213G), that has been shown to be active *in vitro*, has an extended half-life (approximately 24 hours) and reaches plasma concentrations approximately four times higher than those of silodosin. *In vitro* data indicate that silodosin does not have the potential to inhibit or induce cytochrome P450 enzyme systems.

Elimination

Following oral administration of 14C-labelled silodosin, the recovery of radioactivity after 7 days was approximately 33,5 % in urine and 54,9 % in faeces. Body clearance of silodosin was approximately 0,28 l/h/kg. Silodosin is excreted mainly as metabolites, very low amounts of unchanged drug are recovered in urine. The terminal half-life of parent drug and its glucuronide is approximately 11 hours and 18 hours, respectively.

Special populations

Elderly:

Exposure to silodosin and its main metabolites does not change significantly with age, even in subjects of age over 75 years.

Paediatric population:

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

Hepatic impairment:

In a single-dose study, the pharmacokinetics of silodosin was not altered in nine patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), compared to nine healthy subjects. Results from this study should be interpreted with caution, since enrolled patients had normal biochemistry values, indicating normal metabolic function, and they were classified as having moderate liver impairment based on ascites and hepatic encephalopathy.

The pharmacokinetics of silodosin in patients with severe hepatic impairment has not been studied.

Renal impairment:

In a single-dose study, exposure to silodosin (unbound) in subjects with mild (n=8) and moderate renal impairment (n=8) resulted, on average, in an increase of Cmax (1,6-fold) and AUC (1,7-fold) relative to subjects with normal renal function (n=8). In subjects with severe renal impairment (n=5) 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.

Plasma level monitoring in a Phase III clinical study showed that levels of total silodosin after 4 weeks of treatment did not change in patients with mild impairment (n=70), compared to patients with normal renal

function (n=155), while the levels were doubled on average in patients with moderate impairment (n=7).

A review of safety data of patients enrolled in all clinical studies does not indicate that mild renal impairment (n=487) poses an additional safety risk during silodosin therapy (such as an increase in dizziness or orthostatic hypotension) as compared to patients with normal renal function (n=955). Accordingly, no dose adjustment is required in patients with mild renal impairment. Since only limited experience exists in patients with moderate renal impairment (n=35), a lower starting dose of 4 mg is recommended. In patients with severe renal impairment administration of SILDOS is not recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin

Glycerol

Iron

Mannitol

Printing ink – black

Sodium

Starch, Pregelatinised (Maize)

Titanium Dioxide

Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

The capsules are provided in PVC/PVDC/aluminium foil blisters,

packed in cartons.

Packs of 5, 10, 20, 30, 50, 90, 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

SILDOS 4 mg: 54/32.2/0107

SILDOS 8 mg: 54/32.2/0108

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2023

10. DATE OF REVISION OF THE TEXT