PROPOSED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SILODYX 4 mg hard gelatin capsule

SILODYX 8 mg hard gelatin capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SILODYX 4 mg

Each hard gelatin capsule contains 4 mg silodosin.

Contains sugar: mannitol 132,4 mg per capsule.

SILODYX 8 mg

Each hard gelatin capsule contains 8 mg silodosin.

Contains sugar: mannitol 264,8 mg per capsule.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin capsules.

SILODYX 4 mg Opaque yellow hard gelatine capsule, size 3, containing white to pale yellowish fine particles and/or powder.

SILODYX 8 mg Opaque white hard gelatine capsule, size 0, containing white to pale yellowish fine particles and/or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended dose is one capsule of **SILODYX 8 mg** daily. For special patient populations, one

capsule of **SILODYX 4 mg** daily is recommended (see below).

Elderly patients

No dose adjustment is required in the elderly (see section 5.2).

Renal impairment

No dose adjustment is required for 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).

Children and adolescents

There is no relevant use of **SILODYX** in children and adolescents in the indication.

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 of **SILODYX** (see 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 **SILODYX** 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 **SILODYX**, 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 in rare cases 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 **SILODYX** is not recommended.

Renal impairment

The use of **SILODYX** in patients with severe renal impairment (CLCR <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 **SILODYX** 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 **SILODYX**, 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 **SILODYX** leads to a decrease in the amount of semen released during orgasm that may temporarily affect male fertility. This effect disappears after discontinuation of **SILODYX** (see section 4.6).

Excipient warning

SILODYX capsules contain mannitol and may have a laxative effect.

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 ciclosporin) 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 **SILODYX** 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 or ritonavir or ciclosporin) is not recommended.

When **SILODYX** 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 **SILODYX** and maximum doses of sildenafil or tadalafil. In a placebo-controlled study in 24 subjects 45 - 78 years of age receiving **SILODYX**, 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 **SILODYX** 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 **SILODYX** 8 mg once daily. No dose adjustment is required.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

Not applicable, as **SILODYX** 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 **SILODYX** (see section 4.8), due to the pharmacodynamic properties of **SILODYX**. 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

SILODYX 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 **SILODYX** will affect them.

4.8 Undesirable effects

a. Summary of the safety profile

The safety of **SILODYX** has been evaluated in four Phase II-III double-blind controlled clinical studies (with 931 patients receiving **SILODYX** 8 mg once daily and 733 patients receiving placebo) and in two long-term open-label extension phase studies. In total, 1,581 patients have received **SILODYX** at a dose of 8 mg once daily, including 961 patients exposed for at least 6 months and 384 patients exposed for 1 year.

The most frequent adverse reactions reported with **SILODYX** in placebo-controlled clinical studies and during long-term use were ejaculatory disorders such as retrograde ejaculation and anejaculation (ejaculatory volume reduced or absent), with a frequency of 23 %. This may temporarily affect male fertility. It is reversible within a few days upon discontinuation of treatment (see section 4.4).

b. Tabulated summary of adverse reactions

In the table below, adverse reactions reported in all clinical studies and in the worldwide post-marketing

experience for which a reasonable causal relationship exists are listed by MedDRA system organ class and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (frequency cannot be estimated from available data). Within each frequency grouping the observed adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Very rare	Allergic-type reactions including facial swelling, swollen tongue and pharyngeal oedema[1]
Psychiatric disorders	Uncommon	Libido decreased
Nervous system disorders	Common	Dizziness
	Rare	Syncope Loss of consciousness[1]
Cardiac disorders	Uncommon	Tachycardia[1]
	Rare	Palpitations[1]
Vascular disorders	Common	Orthostatic hypotension
	Uncommon	Hypotension[1]
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Nausea Dry mouth
Hepato-biliary disorders	Uncommon	Abnormal liver function tests[1]
Skin and subcutaneous tissue disorders	Uncommon	Skin rash[1] Pruritus[1] Urticaria[1] Drug eruption[1]

MedDRA system organ class	Frequency	Adverse reactions
Reproductive system and breast disorders	Very common	Ejaculatory disorders, including retrograde ejaculation, anejaculation
	Uncommon	Erectile dysfunction
Injury, poisoning and procedural complication	Not known	Intraoperative Floppy Iris Syndrome

[1] – adverse reactions from spontaneous reporting in the worldwide post-marketing experience (frequencies calculated from events reported in Phase I-IV clinical trials and non-interventional studies)

c. Description of selected adverse reactions

Orthostatic hypotension

The incidence of orthostatic hypotension in placebo-controlled clinical studies was 1,2 % with silodosin and 1,0 % with placebo. 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 18.10 Medicines acting on the reno-urinary and genital system: Others.

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

Mechanism of action

Silodosin is 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 (BPH).

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 $\alpha_{1A}\alpha_{1B}$ binding ratio of silodosin (1621) is extremely high.

Clinical efficacy and safety

In a Phase II dose-finding, double-blind, placebo-controlled clinical study with silodosin 4 or 8 mg once daily, a greater improvement in American Urologic Association (AUA) symptom index score was observed with silodosin 8 mg (-6,8 ± 5,8; n = 90; p = 0,0018) and silodosin 4 mg (-5,7 ± 5,5; n = 88; p = 0,0355) as compared to placebo (-4,0 ± 5,5; n = 83).

Over 800 patients with moderate to severe symptoms of BPH (International Prostate Symptom Score, IPSS, baseline value ≥13) received silodosin 8 mg once daily in two Phase III placebo-controlled clinical studies conducted in the United States and in one placebo- and active-controlled clinical study conducted in Europe. In all studies, patients who did not respond to placebo during a 4-week placebo run-in phase were randomised to receive the study treatment. In all studies, patients treated with silodosin had a greater decrease in both storage (irritative) and voiding (obstructive) symptoms of BPH as compared to placebo as assessed after 12 weeks of treatment.

Data observed in the Intent-to-treat populations of each study are shown below:

Study	Treatment area	No of patients	IPSS Total score			IPSS Irritative symptoms		IPSS Obstructive symptoms	
			Baseline value (±SD)	Change from baseline	Difference (95 % CI) vs placebo	Change from baseline	Difference (95 % CI) vs placebo	Change from baseline	Difference (95 % CI) vs placebo
US-1	Silodisin Placebo	233 228	22 ± 5 21 ± 5	-6,5 -3,6	-2,8* (-3,9; -1,7)	-2,3 -1,4	-0,9* (-1,4; -0,4)	-4,2 -2,2	-1,9* (-2,6; -1,2)
US-2	Silodisin Placebo	233 229	21 ± 5 21 ± 5	-6,3 -3,4	-2,9* (-4,0; -1,8)	-2,4 -1,3	-0,9* (-1,4, -0,4)	-4.2 -2,2	-1,9* (-2,6; -1,2)
Europe	Silodisin Tamsulosin Placebo	371 376 185	19 ± 4 19 ± 4 19 ± 4	-7,0 -6,7 -4,7	-2,3* (-3,2; -1,4) -2,0* (-2,9; -1,1)	-2,5 -2,4 -1,8	-0,7* (-1,1; -0,2) -0,6* (-1,1; -0,2)	-4,5 -2,2 -2,9	-1,7* (-2,2; -1,1) -1,4* (-2,0; -0,8)

* p<0,001 vs Placebo; ° p =0,002 vs Placebo

In the active-controlled clinical study conducted in Europe, silodosin 8 mg once daily was shown to be non-inferior to tamsulosin 0.4 mg once daily: the adjusted mean difference (95 % CI) in the IPSS Total Score between treatments in the per-protocol population was 0,4 (-0,4 to 1,1). The responder rate (i.e. improvement in the IPSS total score by at least 25 %) was significantly higher in the silodosin (68 %) and tamsulosin group (65 %), as compared to placebo (53 %).

In the long-term open-label extension phase of these controlled studies, in which patients received silodosin for up to 1 year, the symptom improvement induced by silodosin at week 12 of treatment was maintained over 1 year.

In a Phase IV clinical trial performed in Europe, with a mean baseline IPSS total score of 18,9 points, 77,1 % were responders to silodosin (as assessed by a change from baseline in the IPSS total score

of at least 25 %). Approximately half of the patients reported an improvement in the most bothersome symptoms complained at baseline by the patients (i.e. nocturia, frequency, decreased stream, urgency, terminal dribbling and incomplete emptying), as assessed by the ICS-male questionnaire.

No significant reduction in supine blood pressure was observed in all clinical studies conducted with silodosin.

Silodosin 8 mg and 24 mg daily had no statistically significant effect on ECG intervals or cardiac repolarisation relative to placebo.

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 medicine 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), which 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 ^{14}C-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 silodosin are recovered in urine. The terminal half-life of parent medicine 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 renal impairment (n=8) and moderate renal impairment (n=8) resulted, on average, in an increase of C_{max} (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 in exposure was 2,2-fold for C_{max} 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 **SILODYX** is not recommended.

5.3 Pre-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, carcinogenic, mutagenic and teratogenic potential. Effects in animals (affecting the thyroid gland in rodents) were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use. (1)

In male rats, decreased fertility was observed from exposures which were approximately twice the exposure at the maximum recommended human dose. The observed effect was reversible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Magnesium stearate

Mannitol (E421)

Pregelatinised starch (maize)

Sodium lauryl sulphate

Capsule shell:

Gelatin

Titanium dioxide (E171)

Yellow iron oxide (E172) – 4 mg capsule

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package in order to protect from light and moisture. Do not remove blisters from carton until required for use.

6.5 Nature and contents of container

The capsules are provided in opaque white PVC/PVDC/aluminium foil blisters.

Pack sizes available:

5 capsules (one blister per carton)

10 capsules (one blister per carton)

20 capsules (two blisters per carton)

30 capsules (three blisters per carton)

50 capsules (five blisters per carton)

90 capsules (nine blisters per carton)

100 capsules (ten blisters per carton)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

MIDRAND

8 REGISTRATION NUMBERS

SILODYX 4 mg: 45/32.2/0118

SILODYX 8 mg: 45/32.2/0119

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2013

10 DATE OF REVISION OF THE TEXT

15 September 2022

SILODYX 4 mg

NAMIBIA:
Scheduling status: NS2
Registration no.: 16/34/0002

SILODYX 8 mg

NAMIBIA:
Scheduling status: NS2
Registration no.: 16/34/0003