PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MAKDOSIN 4 mg hard gelatin capsule

MAKDOSIN 8 mg hard gelatin capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAKDOSIN 4 mg: Each capsule contains 4 mg silodosin.

Contains sugar: Mannitol (133.35 mg)

MAKDOSIN 8 mg: Each capsule contains 8 mg silodosin.

Contains sugar: Mannitol (266.7 mg)

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard Gelatin Capsules.

MAKDOSIN 4 mg Opaque white cap/ opaque white body size “3” capsules containing white to off white powder with ‘I 87’ on body imprinted with gold ink.

MAKDOSIN 8 mg Opaque white cap/ opaque white body size “1” capsules containing white to off white powder with ‘I 88’ on body imprinted with green ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAKDOSIN 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 **MAKDOSIN** 8 mg daily. For special patient populations, one capsule of **MAKDOSIN** 4 mg daily is recommended (see below).

Elderly patients:

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

Renal impairment:

For patients with mild renal impairment (CLCR ≥ 50 to ≤ 80 ml/min), no dose adjustment is required.

An initial dose of 4 mg once daily is recommended in patients with moderate renal impairment (CLCR ≥ 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.

MAKDOSIN should not be used in patients with severe renal impairment (CLCR < 30 ml/min) (see sections 4.4 and 5.2).

Hepatic impairment:

No dose adjustment is required for patients with mild to moderate hepatic impairment. **MAKDOSIN** should not be used in patients with severe hepatic impairment, as no data are available (see sections 4.4 and 5.2).

Children and adolescents:

There is no relevant indication for use of **MAKDOSIN** in children and adolescents.

Method of administration:

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 the silodosin or to any of the excipients of **MAKDOSIN** listed in section 6.1

4.4 Special warnings and precautions for use

Intraoperative Floppy Iris Syndromes (IFIS): IFIS (a variant of small pupil syndrome) has been observed during cataract surgery in some patients on **α1-blockers or previously on α1-blockers**. This may lead to increased procedural complications during the operation.

The commencement of therapy with **MAKDOSIN** is not recommended in patients soon to undergo cataract surgery. Discontinuing treatment with an α1-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 **MAKDOSIN**, in order to ensure that appropriate measures will be in place to manage IFIS during surgery.

Orthostatic effects:

A decrease in blood pressure can occur which may result in 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 **MAKDOSIN** is not recommended.

Renal impairment:

The use of **MAKDOSIN** 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 **MAKDOSIN** 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, to rule out the presence of carcinoma of the prostate, patients thought to have BPH should be examined prior to starting therapy with **MAKDOSIN**. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed prior to treatment and at regular intervals afterwards.

Treatment with **MAKDOSIN** leads to a decrease in the amount of semen released during orgasm that may temporarily affect male fertility. This effect disappears after discontinuation of **MAKDOSIN** (see section 4.4. Fertility)

Fertility:

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

Contains mannitol and may have a laxative effect.

This medicine contains less than 1 mmol sodium per tablet, that is to say essentially 'sodium-free'

4.5 Interaction with other medicines and other forms of interaction

Silodosin as in **MAKDOSIN** is metabolised extensively, mainly via CYP3A4, alcohol dehydrogenase and UGT2B7. Silodosin as in **MAKDOSIN** is also a substrate for P-glycoprotein. Substances that inhibit or induce these enzymes and transporters may affect the plasma concentrations of silodosin and it's active metabolite.

Alpha-blockers:

The concomitant use of other α-adrenoreceptors antagonists is not recommended since there is inadequate information about the safe use of **MAKDOSIN** in association with other α-adrenoreceptors antagonists

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).

MAKDOSIN should not be used concomitantly with potent CYP3A4 inhibitors (such as ketoconazole, itraconazole or ritonavir).

When **MAKDOSIN** is co-administered with a CYP3A4 inhibitor of moderate potency such as diltiazem, an increase in silodosin AUC of approximately 30% may be observed, but Cmax and half-life may not be affected. This change is clinically not relevant and no dose adjustment is required.

PDE-5 Inhibitors:

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

Antihypertensives:

In a 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 and lactation:

MAKDOSIN is intended for male patients only, therefore pregnancy and lactation is not applicable.

Fertility:

In studies, the occurrence of ejaculation with reduced or no semen has been observed during treatment with silodosin as in **MAKDOSIN** (see section 4.4), due to the pharmacodynamic properties of **MAKDOSIN**. 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

Patients should be informed about possible occurrence of symptoms related to postural hypotension (such as dizziness) and should be cautioned about driving or operating machines until they know how **MAKDOSIN** will affect them.

4.8 Undesirable effects

Summary of the reported safety profile

The most frequent adverse reactions were ejaculatory disorders, such as retrograde ejaculation and anejaculation. This may temporarily affect male fertility. It is reversible within a few days upon discontinuation of treatment. (See Section 4.4).

Tabulated summary of adverse events

System Organ Class	Frequency	Undesirable effects
Psychiatric disorders:	Less frequent	Libido decreased
Nervous system disorders:	Frequent:	Dizziness
	Frequency unknown	Syncope
Vascular disorders:	Frequent:	Orthostatic hypotension,
	Less frequent	hypotension
Respiratory, thoracic and mediastinal disorders:	Frequent	Nasal congestion
Gastrointestinal disorders:	Frequent:	Diarrhoea
	Less frequency:	Nausea, dry mouth
Reproductive system and breast disorders:	Frequent:	Retrograde ejaculation, anejaculation
	Less frequent:	Erectile dysfunction
Immune system disorders:	Less frequent:	Allergic type reactions including facial swelling, swollen tongue and pharyngeal oedema
Cardiac disorders:	Less frequent:	Tachycardia, palpitations

System Organ Class	Frequency	Undesirable effects
Hepatobiliary disorders:	Less frequent:	Abnormal liver function
Skin and subcutaneous tissue disorders:	Less frequent	Skin rash, pruritus, urticaria, drug eruption
Injury, poisoning and procedural complication:	Frequency unknown:	Intraoperative Floppy Iris Syndrome

Description of selected adverse reactions

Orthostatic hypotension:

The incidence of orthostatic hypotension was observed in placebo-controlled studies. Orthostatic hypotension may 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

Silodosin as in **MAKDOSIN** 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 **MAKDOSIN** lead to hypotension, cardiovascular support has to be provided. Dialysis is unlikely to be of significant benefit since **MAKDOSIN** is highly (96,6%) protein bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical groups: A. 32.2 Other

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

Mechanism of action

Silodosin is selective for α1A-adrenoreceptors that are primarily located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Blockade of these α1-A-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 α1-B-adrenoreceptors that are primarily located in the cardiovascular system. It has been demonstrated in vitro that the α1A: α1B binding ratio of silodoosin (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 medicine. 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 Cmax by approximately 30%, increases tmax by approximately 1 hour and has little effect on AUC.

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 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 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 it’s main metabolites does not change significantly with age, even in subjects of age over 75 years.

Paediatric:

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

Hepatic impairment:

In a study, patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), 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 studies, exposure to silodosin (unbound) in patients with mild renal impairment (n = 8) and moderate renal impairment (n = 8) resulted, in an increase of Cmax (1,6 fold) and AUC (1,7-fold) relative to subjects with normal renal function (n = 8).

In patients with severe renal impairment increase (n = 5) in exposure was 2,2-fold for Cmax and 3,7-fold for AUC. Exposure to the main metabolites, silodosin glucuronide and KMD3293, increased.

Plasma levels of silodosin in patients with moderate renal impairment may double after 4 weeks of treatment.

Studies do not indicate that mild renal impairment 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. Accordingly, no dose adjustment is required in patients with mild renal impairment. Since only limited experience exists in patients with moderate renal impairment, a lower starting dose of 4 mg is recommended. In patients with severe renal impairment, administration of **MAKDOSIN** is not recommended.

5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MAKDOSIN 4 mg

Capsule content: magnesium stearate, pregelatinized starch and sodium lauryl sulphate.

Capsule shell: gelatin, titanium dioxide (E171) and sodium lauryl sulphate

Contains sugar: Mannitol (133.35 mg)

MAKDOSIN 8 mg

Capsule content: magnesium stearate, pregelatinized starch and sodium lauryl sulphate.

Capsule shell: gelatin, titanium dioxide (E171) and sodium lauryl sulphate.

Contains sugar: Mannitol (266.7 mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the manufacturing date for container pack & blister pack.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

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

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

HDPE container pack:

Capsules are packed in 60 ml round, white, HDPE container, 33 mm neck finish with 33 mm child resistant closure, white HS 123 white printed liner.

Capsules are packed in 40 ml or 60 ml round, white, HDPE container, 33 – 400 neck finish with 33 mm child resistant closure with pulp and heat seal liner.

Pack size: 30’s, 90’s

Blister Pack:

Capsules are packed in cold form laminate, 25 µm OPA/45 µm Aluminum foil/60 µm PVC and Plain 25 µm Aluminum foil/6-8 gsm HSL as the lidding material.

Pack size: 5's, 10's, 20's, 30's, 50's, 90's and 100's

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

MAKDOSIN 4 mg: 56/32.2/0319

MAKDOSIN 8 mg: 56/32.2/0320

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2023

10. DATE OF REVISION OF THE TEXT

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