PROFESSIONAL INFORMATION FOR MAKLITIO 20 MG

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MAKLITIO 20 MG (film-coated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAKLITIO 20 MG

Each film-coated tablet contains Sildenafil citrate equivalent to 20mg active base.

Sugar free.

Excipients:

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Oral film-coated tablet.

MAKLITIO 20 MG

White to off white, round shaped, film coated tablets debossed with 'N7' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of pulmonary arterial hypertension. **MAKLITIO 20 MG** has been shown to improve exercise ability and to reduce mean pulmonary arterial pressure.

4.2 Posology and method of administration

Posology:

Use in adults:

The recommended dose is 20 mg three times a day.

Efficacy of **MAKLITIO 20 MG** at a dose of 20 mg three times a day has not been established in a sufficient number of patients beyond 12 weeks of treatment.

Special populations

Use in the elderly:

Dosage adjustments are not required in elderly patients.

Use in patients with impaired renal function:

Dose adjustments are not required in patients with mild to moderate renal impairment (see Section 4.3).

Use in patients with impaired hepatic function:

Dose adjustments are not required in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). Patients with severe hepatic impairment (Child-Pugh class C) have not been studied (see Section 4.3).

Paediatric population:

Safety and effectiveness of **MAKLITIO 20 MG** have not yet been demonstrated in children.

Use in patients using other medicines:

Co-administration of erythromycin or saquinavir and more potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) with **MAKLITIO 20 MG** is contraindicated (see Section 4.5).

Dose adjustments of **MAKLITIO 20 MG** may be required when co-administered with bosentan or other CYP3A4 inducers (see Section 4.5).

Method of administration

For oral use.

MAKLITIO 20 MG should be taken approximately 6 to 8 hours apart with or without food.

4.3 Contraindications

- Use of **MAKLITIO 20 MG** is contraindicated in patients with a known hypersensitivity to sildenafil or any excipient of **MAKLITIO 20 MG** listed in Section 6.1.
- Consistent with its known effects on the nitric oxide/cGMP pathway (see Section 5), **MAKLITIO 20 MG** was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its administration to patients who are concurrently using nitric oxide donors, organic nitrates or organic nitrites in any form

either regularly or intermittently is therefore contraindicated. Medical practitioners should discuss with patients the contraindication of **MAKLITIO 20 MG** with concurrent organic nitrates.

- Concomitant use of **MAKLITIO 20 MG** with potent cytochrome P450 3A4 inhibitors e.g. ritonavir, erythromycin, saquinavir, ketoconazole and itraconazole is contraindicated.
- The use of **MAKLITIO 20 MG** is contraindicated in patients with severe hepatic impairment and patients with severe impairment of renal function (creatinine clearance < 30 mL/min).
- Patients with a systemic blood pressure of under 90/50 mmHg.

4.4 Special warnings and precautions for use

There is no controlled clinical data on the safety or efficacy of sildenafil as in **MAKLITIO 20 MG** in the following groups; if prescribed, this should be done with caution

- Patients who have suffered a myocardial infarction, stroke, or life-threatening dysrhythmia within the last 6 months.
- Patients with resting hypertension (BP > 170/110 mmHg).
- Patients with cardiac failure or coronary artery disease causing unstable angina.
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
- Patients with severe hepatic impairment (see Section 4.3).

Sildenafil as in **MAKLITIO 20 MG** has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers. Medical practitioners should carefully consider whether their patients with certain underlying conditions could be affected adversely by such vasodilatory effects, for example, patients with a low blood pressure, patients with fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction (see section 4.3).

It was reported that in post-marketing experience with sildenafil (the active ingredient of **MAKLITIO 20 MG**) for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular dysrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, and hypertension, have been reported. Most, but not all, of these patients had pre-existing cardiovascular risk factors.

Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are

related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

MAKLITIO 20 MG should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of any reaction that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result (see section 4.8).

Sildenafil should not be used in patients with pulmonary hypertension secondary to sickle cell anaemia.

Concomitant administration of sildenafil as in **MAKLITIO 20 MG** to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals (see Section 4.5). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating **MAKLITIO 20 MG** treatment. Medical practitioners should advise patients what to do in the event of postural hypotensive symptoms.

Sildenafil as in **MAKLITIO 20 MG** has no effect on bleeding time, including during co-administration with aspirin. In vitro studies with human platelets indicate that sildenafil as in **MAKLITIO 20 MG** potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, **MAKLITIO 20 MG** should be administered with caution to these patients.

It was reported that the incidence of epistaxis was higher in patients with pulmonary arterial hypertension secondary to connective tissue disease (sildenafil 12,9 %, placebo 0 %) than in primary pulmonary hypertension patients (sildenafil 3,0 %, placebo 2,4 %) and was higher in sildenafil - treated patients treated with concomitant oral vitamin K antagonist (8,8 % versus 1,7 % not treated with concomitant vitamin K antagonist).

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease. Since there are no clinical data on administration of sildenafil to patients with pulmonary veno-occlusive disease, administration of **MAKLITIO 20 MG** to such patients is not recommended.

Non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision or loss of vision, has been reported post-marketing with the use of PDE5 inhibitors, including sildenafil. Most of these patients had risk factors such as low cup to disc ratio ("crowded disk"), age over 50, diabetes, hypertension, coronary artery

disease, hyperlipidaemia and smoking. It is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. Medical practitioners should discuss with patients the increased risk of NAION in individuals who have already experienced NAION.

The patients should be advised to seek immediate medical attention in case of sudden vision loss.

The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitor products, including sildenafil 25 or 50 mg used for erectile dysfunction, has not been studied in PAH patients and such concomitant use is not recommended (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on sildenafil (the active ingredient of **MAKLITIO 20 MG**):

In vitro studies:

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies:

Co-administration of oral sildenafil and intravenous epoprostenol has been evaluated (see sections 4.8 and 5.1).

The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg,ambrisentan, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration.

The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitors has not been studied in pulmonaryarterial hypertension patients (see section 4.4).

It was reported that population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary arterial hypertension. The exposure to sildenafil in patients on CYP3A4 substrates and CYP3A4 substrates plus beta-blockers was 43 % and 66 % higher, respectively, compared to patients not receiving these medicine classes.

Sildenafil exposure was 5-fold higher at a dose of 80 mg three times a day compared to the exposure at a dose of 20 mg three times a day. This concentration range covers the increase in sildenafil exposure observed

in specifically designed medicine interaction studies with CYP3A4 inhibitors (except more potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole, ritonavir).

It was reported that in a study of healthy male volunteers co-administration of the endothelin antagonist bosentan, which is a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19, at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in a 62,6 % decrease of sildenafil AUC and a 55,4 % decrease in sildenafil C_{max}. The combination of both medicines did not lead to clinically significant changes of blood pressure (supine and standing) and was well tolerated in healthy volunteers.

It was reported that cimetidine (800 mg), a non-specific CYP3A4 inhibitor, caused a 56 % increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

It was reported that when a single 100 mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg two times daily for 5 days), there was a 182 % increase in sildenafil systemic exposure (AUC) (see Section 4.3).

CYP3A4 inhibitors like clarithromycin and telithromycin are expected to have an effect in between that of ritonavir and CYP3A4 inhibitors like saquinavir or erythromycin, a seven-fold increase in exposure is assumed.

In addition, co-administration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1 200 mg three times daily) with sildenafil (100 mg single dose) resulted in a 140 % increase in sildenafil C_{max} and a 210 % increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics (see Section 4.2). The most potent CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have still greater effects similar to those of ritonavir. (see Section 4.3).

It was reported that co-administration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300 % (4-fold) increase in sildenafil C_{max} and a 1 000 % (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics (see Section 4.2). Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is contraindicated.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Co-administration of oral contraceptives (ethinyloestradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil. It was reported that in normal healthy male volunteers, there was no evidence

of an effect of azithromycin (500 mg daily for3 days) on the AUC, C_{max}, T_{max} elimination rate constant or subsequent half-life of sildenafil or its major circulating metabolite.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil. No dose adjustment is required but the concomitant use of sildenafil and grapefruit juice is not recommended.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil (see section 4.3).

Efficacy of sildenafil should be closely monitored in patients using concomitant potent CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, St John's wort and rifampicin.

Effects of sildenafil on other medicines:

In vitro studies:

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 > 150 µM).

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:

It was reported that no significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil had no significant effect on atorvastatin exposure (AUC increased 11 %), suggesting that sildenafil does not have a clinically relevant effect on CYP3A4.

No interactions were observed between sildenafil (100 mg single dose) and acenocoumarol. Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

It was reported that sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

It was reported that in a study of healthy volunteers, sildenafil at steady state (80 mg three times a day) resulted in a 49,8% increase in bosentan AUC and a 42 % increase in bosentan C_{max} (125 mg twice daily).

No interaction was seen when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additive reduction on supine blood pressure (systolic, 8 mmHg; diastolic, 7 mmHg) was of a similar magnitude to that seen when sildenafil was administered alone to healthy volunteers (see Section 5.2).

It was reported that in three specific medicine interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilised on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilised on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see Section 4.4).

Sildenafil was shown to potentiate the hypotensive effect of acute and chronic nitrates. Therefore, use of nitric oxide donors, organic nitrates or organic nitrites in any form, either regularly or intermittently with sildenafil is contraindicated (see Section 4.3).

Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated (see section 4.3).

Sildenafil had no clinically significant impact on the plasma levels of oral contraceptives (ethinyloestradiol 30 µg and levonorgestrel 150 µg).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception in males and females.

Due to lack of data on effects of sildenafil in pregnant women, **MAKLITIO 20 MG** is not recommended for women of childbearing potential unless also using appropriate contraceptive measures.

Pregnancy

There are no data from the use of sildenafil in pregnant women. Animal studies do not indicate direct or indirect effects with respect to pregnancy and embryonal' foetal development. Studies in animals have shown toxicity to postnatal development.

Due to lack of data, **MAKLITIO 20 MG** should not be used in pregnant women.

Breast-feeding

It is not known whether **MAKLITIO 20 MG** enters the breast milk. **MAKLITIO 20 MG** should not be administered to breastfeeding mothers.

Fertility

Non-clinical data revealed no special hazard for humans based on conventional studies of fertility.

4.7 Effects on ability to drive and use machines

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware how they react to **MAKLITIO 20 MG** and exercise caution before driving, operating hazardous machinery or performing hazardous tasks.

4.8 Undesirable effects

The most frequently reported adverse reactions that occurred on sildenafil than on placebo were headache, flushing, dyspepsia, back pain, diarrhoea and limb pain.

Tabulated summary of adverse events

System organ class	**Frequency**	**Undesirable effect**
Infections and infestations	Frequent	Cellulitis, influenza, sinusitis not otherwise specified (NOS),
Blood and lymphatic system disorders	Frequent	Anaemia NOS
	Frequency unknown	Leukopenia[1].
Immune system disorders	Frequency unknown	shock[1], allergic reaction[1]
Metabolic and nutrition disorders	Frequent	Fluid retention
	Frequency unknown	Thirst[1], oedema[1], gout[1], unstable diabetes[1], hyperglycaemia[1], peripheral oedema[1], hyperuricemia[1], hypoglycaemic reaction[1], and hypernatremia[1].
Psychiatric disorders	Frequent	Insomnia, anxiety
	Frequency unknown	Depression[1], somnolence[1], abnormal dreams[1]

System organ class	Frequency	Undesirable effect
Nervous system disorders	Frequent	Headache, Migraine NOS, tremor, paraesthesia, burning sensation NOS, hypoaesthesia
	Frequency unknown	Ataxia[1], hypertonia[1], neuralgia[1], neuropathy[1], tremor[1] and reflexes decreased,[1] dizziness,[1] syncope[1]
Eye disorders	Frequent	Visual acuity reduced, retinal haemorrhage, visual disturbance NOS, photophobia, diplopia, chromatopsia, cyanopsia, abnormal sensation in eye, eye irritation, hyperaemia
	Frequency unknown	Non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion, visual field defect, abnormal vision (Mild and transient. Predominantly colour tinge to vision, but also increased perception of light or blurred vision)[1], temporary vision loss/decreased vision[1], ocular redness or bloodshot appearance[1], ocular burning[1], ocular swelling/pressure[1], increased intraocular pressure[1], retinal vascular disease or bleeding[1], vitreous detachment/traction and paramacular oedema[1]. Conjunctivitis[1], photophobia[1], eye haemorrhage[1], cataract[1], dry eyes and eye pain[1].
Ear and labyrinth disorders	Frequent	Vertigo
	Frequency unknown	Sudden hearing loss, tinnitus[1], deafness[1], ear pain[1].
Cardiac disorder	Frequency unknown	Angina pectoris[1], AV block[1], tachycardia[1], palpitation[1], cardiac arrest[1], heart failure[1], abnormal electrocardiogram[1], cardiomyopathy[1]
Vascular disorders	Frequent	Flushing
	Frequency unknown	Hypotension, postural hypotension[1]
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis, cough, nasal congestion, bronchitis NOS, rhinitis NOS
	Frequency unknown	Asthma[1], dyspnoea[1], laryngitis[1], pharyngitis[1], sinusitis[1], sputum increased[1]

System organ class	Frequency	Undesirable effect
Gastrointestinal disorders	Frequent	Diarrhoea, dyspepsia, Gastritis NOS, gastroenteritis NOS, gastrooesophageal reflux disease, haemorrhoids, abdominal distension
	Frequency unknown	Vomiting[1], glossitis[1], colitis[1], dysphagia[1], gastritis[1], esophagitis[1], stomatitis[1], dry mouth[1], rectal haemorrhage[1], gingivitis[1].
Hepatobiliary disorders	Frequency unknown	Liver function tests abnormal
Skin and subcutaneous tissue disorders	Frequent	Alopecia, erythema, night sweats
	Frequency unknown	Rash, Urticaria[1], herpes simplex[1], pruritus[1], sweating[1], skin ulcer[1], contact dermatitis[1], exfoliative dermatitis[1] photosensitivity reaction[1].
Musculoskeletal and connective tissue disorders	Frequent	Limb pain, myalgia, back pain
	Frequency unknown	Arthritis[1], arthrosis[1], tendon rupture[1], and tenosynovitis[1], bone pain[1], myasthenia[1], synovitis[1].
Renal and urinary disorders	Frequency unknown	Haematuria, cystitis[1], nocturia, urinary frequency[1],urinary incontinence[1]
Reproductive system and breast disorders	Frequent	Gynaecomastia
	Less frequent	Penile haemorrhage, haematospermia
	Frequency unknown	Priapism, erection increased, breast enlargement[1], abnormal ejaculation, genital oedema, anorgasmia
General disorders and administration site conditions	Frequent	Pyrexia
	Frequency unknown	Face oedema[1], asthenia[1], pain[1], chills[1], accidental fall[1], chest pain[1], accidental injury[1].
Investigations	Frequent	Weight increase

[1]Other side effects reported with sildenafil use not associated with PAH

The overall frequency of discontinuation in sildenafil- treated patients at the recommended daily dose of 20 mg three times a day was low and the same as placebo.

A sudden unilateral or bilateral decrease or loss of hearing (sensorineural deafness) with or without associated vestibular symptoms has been reported with the use of PDE5 inhibitors, including sildenafil.

There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

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

In studies with healthy volunteers, of single doses up to 800 mg, adverse events were similar to those seen at lower doses, but incidence rates were increased. In cases of overdose, supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

Category and Class:A 7.1.5 Vasodilators – peripheral.

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction: ATC code: G04B E03.

5.1 Pharmacodynamic properties

Sildenafil is an oral therapy for pulmonary arterial hypertension.

Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary arterial hypertension this can lead to selective vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies in vitro have shown that sildenafil is selective for PDE5. There is a 10-fold selectivity in isoenzyme affinity for PDE5 over PDE6 which is involved in the photo transduction pathway in the retina.

There is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4 000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase iso form involved in the control of cardiac contractility.

Sildenafil causes mild and transient decreases in systemic blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decrease in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8,3 mmHg. The corresponding change in supine diastolic blood pressure was

5,3 mmHg. After chronic dosing of 80 mg three times a day to healthy male volunteers, the largest average change from baseline of supine systolic blood pressure was a decrease of 9,0 mmHg. The corresponding change in supine diastolic blood pressure was a decrease of 8,4 mmHg.

After chronic dosing of 80 mg three times a day to patients with systemic hypertension the mean change from baseline in systolic and diastolic blood pressure was a decrease of 9,4 mmHg and 9,1 mm Hg respectively.

After chronic dosing of 80 mg three times a day to patients with pulmonary arterial hypertension lesser effects in blood pressure reduction were observed (a reduction in both systolic and diastolic pressure of 2 mmHg). This may be due to improvements in cardiac output secondary to the beneficial effects of sildenafil on pulmonary vascular resistance.

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg three times a day to patients with pulmonary arterial hypertension no clinically relevant effects on the ECG were reported.

In a study of the haemodynamic effects of a single oral 100 mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (> 70 % stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 7 % and 6 % respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9 %. Sildenafil showed no effect on cardiac output and did not impair blood flow through the stenosed coronary arteries.

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the photo transduction cascade of the retina. Sildenafil has no significant effect on visual acuity or contrast sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100 mg) demonstrated no significant changes in visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photo stress).

5.2 Pharmacokinetic properties

Absorption

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability

is approximately 40 % (range 25 – 63 %). After oral three times a day dosing of sildenafil, AUC and C_{max} increase in proportion with dose over the dose range of 20 – 40 mg. After oral doses of 80 mg three times a day slightly more than dose proportional increase in sildenafil plasma levels has been observed.

When sildenafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29 %.

Distribution

The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. After oral doses of 20 mg three times a day, the mean maximum total plasma concentration of sildenafil at steady state is approximately 113 ng/ml. Since sildenafil and its major circulating N-desmethyl metabolite are both approximately 96 % bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 4,52 ng/ml (9,5 nM). Protein binding is independent of total drug concentrations.

Biotransformation

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil.

This metabolite has a PDE selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50 % that of the parent drug. Plasma concentrations of this metabolite are approximately 40 % of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 hours. In patients with pulmonary arterial hypertension, however, the ratio of UK-103,320 to sildenafil is higher. Plasma concentrations of UK-103,320 are approximately 72 % those of sildenafil after 20 mg three times a day dosing (translating into a 36 % contribution to sildenafil's pharmacological effects). The subsequent effect on efficacy is unknown.

Elimination

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3 – 5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

Pharmacokinetics in special patient groups:

Elderly:

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40 % greater than those seen in healthy younger volunteers (18 – 45years).

Renal insufficiency:

In volunteers with mild (CLcr (creatinine clearance) = 50 – 80 ml/min) and

ml/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe (CLcr ≤ 30 ml/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100 %) and C_{max} (88 %) compared to age-matched volunteers with no renal impairment.

Hepatic insufficiency:

In volunteers with hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84 %) and C_{max} (47 %) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

Population pharmacokinetic properties:

Age, gender, race, renal and hepatic function were included as factors in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in pulmonary arterial hypertension patients. The data set available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated to hepatic and renal function. None of the factors related to demographics, hepatic or renal function had a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary arterial hypertension. However, CYP3A4 substrates alone reduced the apparent clearance of sildenafil by 22,3 % and in combination with beta-blockers by 37,4 %. No other factors had a statistically significant influence on sildenafil pharmacokinetics. In patients with pulmonary arterial hypertension, the average steady state concentrations were 20 – 50% higher over the investigated dose range of 20 – 80 mg three times a day compared to healthy volunteers. There was a doubling of the C_{min} compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary arterial hypertension compared to healthy volunteers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, dibasic calcium phosphate dehydrate hypromellose, magnesium stearate, microcrystalline cellulose and film coating containing hypromellose, titanium dioxide and triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months for container pack and 48 months for blister pack from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

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

6.5 Nature and contents of container

HDPE container:

Round, white, HDPE container (30 ml**)** with 28 mm neck finish, containing 90 tablets, closed with white a polypropylene child resistant with pulp and heat seal liner and packed in a pre-printed unit carton.

Blister pack:

Clear 250 µ PVC/ 60 gsmPVdC as the forming material and silver coloured plain 25µ aluminium foil/ 6-8 gsm HSL as the lidding material, packed in a pre-printed unit carton.

Pack sizes 10s, 28's, 30's and 90's.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product 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)

MAKLITIO 20 MG: 51/7.1.5/0406

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 JULY 2022

10. DATE OF REVISION OF THE TEXT

30 November 2023

PM0081

Vanita Rajool

Digitally signed by Vanita Rajool
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Date: 2023.12.18 15:39:19 +02'00'