1.3.1.1.1 Approved Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SILDENAFIL VIATRIS film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SILDENAFIL VIATRIS film-coated tablet contains sildenafil citrate equivalent to sildenafil 20 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

A white, film coated, round, biconvex tablet debossed with ‘M’ on one side of the tablet and ‘SL over 20’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of pulmonary arterial hypertension (PAH). SILDENAFIL VIATRIS 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. Tablets should be taken approximately 6 to 8 hours apart with or without food.

Efficacy of SILDENAFIL VIATRIS 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 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 SILDENAFIL VIATRIS 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 SILDENAFIL VIATRIS is contraindicated *(see sections 4.3 and 4.5).*

Dose adjustments of SILDENAFIL VIATRIS may be required when co-administered with

bosentan or other CYP3A4 inducers *(see section 4.5)*.

Method of administration

SILDENAFIL VIATRIS tablets are for oral use. (1)

4.3 Contraindications

- Hypersensitivity to sildenafil or to any of the excipients *(see section 6.1)*.
- Co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form due to the hypotensive effects of nitrates *(see sections 4.4 and 4.5)*.

- The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension *(see section 4.4 and 4.5)*.
- Combination with the most potent of the CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, saquinavir) *(see section 4.5)*.
- Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure *(see section 4.4)*.
- The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated:

  -Severe hepatic impairment (Child-Pugh class C).

  -Recent history of stroke or myocardial infarction.

  -Severe hypotension (blood pressure < 90/50 mmHg) at initiation.

  -Severe impairment of renal function (creatinine clearance < 30 mL/min).

4.4 Special warnings and precautions for use

There is no controlled clinical data on the safety or efficacy of SILDENAFIL VIATRIS 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 *(see section 4.3)*.
- 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)*.

Vasodilatory action

SILDENAFIL VIATRIS has systemic vasodilatory properties that resulted in mild and transient decreases in supine blood pressure in healthy volunteers. Medical doctors 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 (e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy) or autonomic dysfunction *(see section 4.3)*.

Cardiovascular risks

In post-marketing experience with sildenafil (the active ingredient of SILDENAFIL VIATRIS) for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina pectoris, sudden cardiac death, ventricular dysrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension, have been reported in temporal association with the use of sildenafil.

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 these factors or to other factors.

Priapism and anatomical penis deformation

SILDENAFIL VIATRIS 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 VIATRIS in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. Priapism is a urological emergency. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result *(see section 4.8)*.

Alpha-blockers

Concomitant administration of SILDENAFIL VIATRIS 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 SILDENAFIL VIATRIS treatment. Medical doctors should advise patients what to do in the event of postural hypotensive symptoms.

Bleeding disorders

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

Vitamin K antagonists

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

Veno-occlusive disease

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 VIATRIS to patients with pulmonary veno-occlusive disease, administration of SILDENAFIL VIATRIS to such patients is not recommended.

Ocular risks

There were indications in a large epidemiological study of an increased risk of retinal detachment during regular use of PDE5 inhibitors.

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 VIATRIS *(see section 4.8)*. 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. In the event of any sudden visual defect or if sudden vision loss occurs in one or both eyes, SILDENAFIL VIATRIS should be stopped immediately, and alternative treatment should be considered. It is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. Medical doctors 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 of SILDENAFIL VIATRIS has not been studied in patients with known hereditary degenerative retinal diseases such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases) and its use in such patients can therefore not be recommended.

Nitrates

SILDENAFIL VIATRIS increases the anti-hypertensive effect of nitrates *(see sections 4.3 and 4.5)*. Patients who suffer acute cardiovascular events must not be treated with nitrates if they have or may have taken sildenafil (as contained in SILDENAFIL VIATRIS), as severe life-threatening hypotension can occur *(see section 4.3)*.

Interaction with guanylate cyclase stimulators

Like PDE5 inhibitors, guanylate cyclase stimulators (such as riociguat) cause changes in intracellular cGMP. Both PDE5 inhibitors and guanylate cyclase stimulators have a vasodilation effect. If the cGMP level rises when the two mechanisms of action combine,

an additive effect on systemic blood pressure can be expected, with an increased risk of symptomatic hypotension *(see section 4.5)*. SILDENAFIL VIATRIS must not be used together with guanylate cyclase stimulators *(see section 4.3)*.

Lactose warning

SILDENAFIL VIATRIS contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take SILDENAFIL VIATRIS.

Use of SILDENAFIL VIATRIS with bosentan

The efficacy of SILDENAFIL VIATRIS in patients already on bosentan therapy has not been conclusively demonstrated *(see section 4.5)*.

Concomitant use with other PDE5 inhibitors

The safety and efficacy of SILDENAFIL VIATRIS when co-administered with other PDE5 inhibitors has not been studied in PAH patients and such concomitant use is not recommended *(see sections 4.3 and 4.5)*.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on sildenafil

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. For dose recommendations, see sections 4.2 and 4.3.

In vivo studies

The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (e.g. 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 VIATRIS when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients *(see section 4.3 and 4.4)*.

Population pharmacokinetic analysis of pulmonary arterial hypertension 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 classes of medicines. 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 with the most potent of the CYP3A4 inhibitors e.g. ketoconazole, itraconazole, ritonavir).

CYP3A4 inducers seemed to have a substantial impact on the pharmacokinetics of sildenafil in pulmonary arterial hypertension patients, which was confirmed in the *in-vivo* interaction study with CYP3A4 inducer bosentan.

Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 %

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.

A population pharmacokinetic analysis of sildenafil data from adult PAH patients in clinical trials including a 12-week study to assess the efficacy and safety of oral sildenafil 20 mg three times a day when added to a stable dose of bosentan (62.5 mg – 125 mg twice a day) indicated a decrease in sildenafil exposure with bosentan co-administration, similar to that observed in healthy volunteers *(see section 4.2 and 4.4)*.

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

Co-administration of 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 administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Based on these pharmacokinetic results co-administration of SILDENAFIL VIATRIS with ritonavir is contraindicated in pulmonary arterial hypertension patients *(see section 4.3)*.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) 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. For dose recommendations, see section 4.2.

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182 % increase in sildenafil systemic exposure (AUC). For dose recommendations, see

section 4.2. In healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max}, T_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. No dose adjustment is required. Cimetidine (800 mg), a cytochrome P450 inhibitor and a non-specific CYP3A4 inhibitor, caused a 56 % increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers. No dose adjustment is required.

The most potent of the CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have effects similar to ritonavir *(see section 4.3)*. CYP3A4 inhibitors like clarithromycin, telithromycin and nefazodone 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. Therefore, dose adjustments are recommended when using CYP3A4 inhibitors *(see section 4.2)*.

The population pharmacokinetic analysis in pulmonary arterial hypertension patients suggested that co-administration of beta-blockers in combination with CYP3A4 substrates might result in an additional increase in sildenafil exposure compared with administration of CYP3A4 substrates alone.

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 VIATRIS and grapefruit juice is not recommended.

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.

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)*.

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

No significant interactions were shown when sildenafil (50 mg) was co-administered 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 acetyl salicylic acid (150 mg).

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

In a study of healthy volunteers, sildenafil at steady state (80 mg three times a day) resulted in a 50 % increase in bosentan AUC and a 42 % increase in bosentan C_{max} (125 mg twice daily). A population pharmacokinetic analysis of data from a study of adult PAH patients on background bosentan therapy (62,5 mg - 125 mg twice a day) indicated an

increase (20 % (95 % CI: 9,8 – 30,8)) of bosentan AUC with co-administration of steady-state sildenafil (20 mg three times a day) of a smaller magnitude than seen in healthy volunteers when co-administered with 80 mg sildenafil three times a day *(see section 4.2 and 4.4)*.

In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.

In three specific 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 light-headedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals *(see section 4.4)*.

Sildenafil (100 mg single dose) did not affect the steady state pharmacokinetics of the HIV protease inhibitor saquinavir, which is a CYP3A4 substrate/inhibitor.

Consistent with its known effects on the nitric oxide/cGMP pathway *(see section 5.1)*, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-

administration with nitric oxide donors or nitrates in any form is therefore contraindicated *(see section 4.3 and 4.5)*.

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of SILDENAFIL VIATRIS in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryonal/foetal development. However, tests on animals have shown toxicity in terms of post-natal development.

Due to lack of data, SILDENAFIL VIATRIS should not be used in pregnant women.

Breast-feeding

There are no adequate and well controlled studies in breastfeeding women. Limited data indicates that sildenafil, as contained in SILDENAFIL VIATRIS and its active metabolites pass into breast milk to a minimal extent. SILDENAFIL VIATRIS should not be administered to breastfeeding mothers.

4.7 Effects on ability to drive and use machines

SILDENAFIL VIATRIS has moderate influence on the ability to drive and use machines.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they might be affected by SILDENAFIL VIATRIS, before driving, using machines or performing hazardous tasks.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions that occurred on SILDENAFIL VIATRIS compared to placebo were headache, flushing, dyspepsia, diarrhoea and pain in extremity.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Cellulitis, influenza, sinusitis not otherwise specified (NOS).
Blood and lymphatic system disorders	Frequent	Anaemia NOS.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Frequent	Fluid retention.
Psychiatric disorders	Frequent	Insomnia, anxiety.
Nervous system disorders	Frequent	Headache, migraine NOS, tremor, paraesthesia, burning sensation NOS, hypoaesthesia
Eye disorders	Frequent	Reduced visual acuity, retinal haemorrhage, visual disturbance NOS, photophobia, diplopia, chromatopsia, cyanopsia, abnormal sensation in eye, eye irritation, blurred vision.
	Not known	Visual field defects, non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision or loss of vision *(see section 4.4)*, retinal vessel occlusion.

Ear and labyrinth disorders	Frequent	Vertigo.
	Not known	Unilateral or bilateral loss of hearing (sensorinearal deafness) with or without associated vestibular symptoms (tinnitus and/or dizziness).
Vascular disorders	Frequent	Flushing.
	Not known	Hypotension, various haemorrhages (eye, cerebral, pulmonary haemorrhage).
Respiratory, thoracic and mediastinal disorders	Frequent	Bronchitis NOS, epistaxis, rhinitis NOS, cough, swelling of the nasal mucosa.
Gastrointestinal disorders	Frequent	Diarrhoea, dyspepsia, gastritis NOS, gastroenteritis NOS, gastroesophageal reflux disease, haemorrhoids, abdominal distension, dry mouth.
Skin and subcutaneous tissue disorders	Frequent	Alopecia, erythema.
	Not known	Rash.
Musculoskeletal and connective tissue disorders	Frequent	Pain in extremity, back pain, myalgia.

Reproductive system and breast disorders	Frequent	Gynaecomastia
	Not known	Prolonged erection, priapism.
General disorders and administration site conditions	Frequent	Pyrexia, night sweats.
Investigations	Frequent	Weight increase

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 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

Signs and symptoms

- In overdose, side effects can be precipitated and/or be of increased severity *(see section 4.8)*.
- In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased.

- At single doses of 200 mg the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, and altered vision) was increased.

Treatment

- In cases of overdose, standard supportive and symptomatic 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

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

Pharmacotherapeutic group: Genito urinary system and sex hormones.

ATC code: G04BE03.

Mechanism of action

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 isoform 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 phototransduction 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 photostress).

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 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 compound. 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, plasma concentrations of N-desmethyl metabolite 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 Populations:

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 (18-45 years).

Renal Insufficiency:

In volunteers with mild (CLcr (creatinine clearance) =50-80 ml/min) and moderate (CLcr=30-49 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 pharmacokinetics:

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

Tablet core:

calcium hydrogen phosphate anhydrous

cellulose microcrystalline

croscarmellose sodium

magnesium stearate

Coating:

HPMC 2910/hypromellose 6 Cp, titanium dioxide (E171), FD & C blue # 2 /indigo carmine aluminium lake, triacetin, FD&C blue # 2/indigo carmine aluminium lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister in the carton until required for use.

6.5 Nature and contents of container

PVC Blister Pack (marketable pack) comprises of clear, transparent, non-toxic PVC on one side and hard tempered aluminium foil (coated with VMCH heat seal lacquer) on the other side.

Suitable number of blister strips will be placed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS SOUTH AFRICA (PTY) LTD

4 Brewery Street

Isando

Johannesburg, 1609

Republic of South Africa

8 REGISTRATION NUMBER

49/7.1.5/1097

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2022

10 DATE OF REVISION OF THE TEXT

14 October 2024