SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

REVATIO® film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of sildenafil, as the citrate.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each REVATIO film-coated tablet contains 0,735 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White to off-white round biconvex film-coated tablets debossed with ‘RVT 20’ on one side and ‘‘VLE’ on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of pulmonary arterial hypertension (PAH). REVATIO has been shown to improve exercise ability and to reduce mean pulmonary arterial pressure.

4.2 Posology and method of administration

Posology

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 REVATIO 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

Elderly population

Dosage adjustments are not required in elderly patients.

Renal impairment

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

Hepatic impairment

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).

Patients using other medicines

Co-administration of erythromycin or saquinavir and most potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) with REVATIO is contraindicated (see section 4.5).

Dose adjustments of REVATIO may be required when co-administered with bosentan or other CYP3A4 inducers (see section 4.5).

Paediatric population

REVATIO is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Method of administration

For oral use.

4.3 Contraindications

- Use of REVATIO is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients of the tablet (listed in section 6.1).
- Consistent with its known effects on the nitric oxide/cGMP pathway, see section 5.1, REVATIO 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 REVATIO with concurrent organic nitrates.
- The co-administration of PDE5 inhibitors, including REVATIO, with guanylate cyclase stimulators, such

as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

- Concomitant use of REVATIO with potent cytochrome P450 3A4 inhibitors e.g. ritonavir, erythromycin, saquinavir, ketoconazole and itraconazole is contraindicated.
- The use of REVATIO 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 REVATIO 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).

Vasodilatory action

REVATIO has systemic vasodilatory properties that resulted in mild and 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).

Cardiovascular risk factors

In post-marketing experience with sildenafil (the active ingredient of REVATIO) 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 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

REVATIO 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 REVATIO in post-marketing experience. In the event of an erection 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).

Alpha-blockers

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

Bleeding disorders

REVATIO has no effect on bleeding time, including during co-administration with aspirin. *In vitro* studies with human platelets indicate that REVATIO potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of REVATIO to patients with bleeding disorders or active peptic ulceration. Therefore, REVATIO 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 (REVATIO 12,9 %, placebo 0 %) than in primary pulmonary hypertension patients (REVATIO 3,0 %, placebo 2,4 %) and was higher in REVATIO-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 REVATIO to patients with pulmonary veno-occlusive disease, administration of REVATIO to such patients is not recommended.

Visual events

A large-scale epidemiological study found evidence of an increased risk of retinal detachment with regular use of PDE5 inhibitors.

Non-arteritic anterior ischaemic optic neuropathy (NAION), a rare condition and a cause of decreased vision or loss of vision, has been reported post-marketing with the use of PDE5 inhibitors, including REVATIO (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, REVATIO should be stopped immediately, and alternative treatment should be considered. 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.

Excipient information

Lactose

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

Use of REVATIO with bosentan

The efficacy of REVATIO in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

Concomitant use with other PDE5 inhibitors

The safety and efficacy of REVATIO when co-administered with other PDE5 inhibitor products has not been studied in PAH patients and such concomitant use is not recommended.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on sildenafil (the active ingredient of REVATIO)

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

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 with the most potent of the CYP3A4 inhibitors e.g. ketoconazole, itraconazole, ritonavir).

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.

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 sections 4.2, 4.4 and 5.1).

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.

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate 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 effects similar to those of ritonavir (see section 4.3).

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 (ethinylestradiol 30 μg and levonorgestrel 150 μg) did not affect the pharmacokinetics of sildenafil.

In normal 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 major circulating metabolite.

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).

In vivo studies

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

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).

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 49,8 %

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 sections 4.2, 4.4 and 5.1).

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 5.1).

In three specific drug-drug 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 REVATIO to patients taking alpha-blocker therapy may lead to symptomatic hypotension in 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 REVATIO is contraindicated (see section 4.3).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of REVATIO in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryonal/foetal development.

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

Breastfeeding

There are no adequate and well controlled studies in lactating women. Data from one lactating woman indicate that sildenafil and its active metabolite N-desmethylsildenafil are excreted into breast milk at very low levels. No clinical data are available regarding adverse events in breastfed infants but amounts ingested would not be expected to cause any adverse effects. Medical practitioners should carefully assess the mother's clinical need for REVATIO and any potential adverse effects on the breastfed child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In the pivotal placebo-controlled study of REVATIO in pulmonary arterial hypertension, a total of 207 patients were treated with REVATIO at daily doses ranging from 20 mg to 80 mg three times a day and 70 patients were treated with placebo. The duration of treatment was 12 weeks.

Tabulated summary of adverse reactions

The most commonly reported adverse drug reactions that occurred (≥ 10 %) on REVATIO than on placebo were headache, flushing, dyspepsia, back pain, diarrhoea and pain in extremity.

The adverse drug reactions that occurred in > 1 % of REVATIO-treated patients and were more common on REVATIO in the pivotal placebo-controlled trial in pulmonary arterial hypertension at doses of 20, 40 or 80 mg three times a day are shown in Table 1.

Table 1: Adverse drug reactions occurring in > 1 % of patients when compared to placebo, in patients on REVATIO (20, 40 or 80 mg three times a day), in the pivotal placebo-controlled trials in pulmonary arterial hypertension.

Reporting frequency: Very common (≥ 1/10); common (≥ 1/100 to < 1/10).

MedDRA System organ class	**Frequency**	**Adverse drug reaction**
Infections and infestations	Common	Cellulitis, influenza, sinusitis not otherwise specified

		(NOS)
Blood and lymphatic system disorders	Common	Anaemia NOS
Metabolism and nutrition disorders	Common	Fluid retention
Psychiatric disorders	Common	Insomnia, anxiety
Nervous system disorders	Very common	Headache
	Common	Migraine NOS, tremor, paraesthesia, burning sensation NOS, hypoaesthesia
Eye disorders	Common	Reduced visual acuity, retinal haemorrhage, visual disturbance NOS, photophobia, diplopia, chromatopsia, cyanopsia, abnormal sensation in eye, eye irritation
Ear and labyrinth disorders	Common	Vertigo
Vascular disorders	Very common	Flushing
Respiratory, thoracic and mediastinal disorders	Common	Bronchitis NOS, epistaxis, rhinitis NOS, cough
Gastrointestinal disorders	Very common	Diarrhoea, dyspepsia
	Common	Gastritis NOS, gastroenteritis NOS, gastroesophageal reflux disease, haemorrhoids, abdominal distension
Skin and subcutaneous tissue disorders	Common	Alopecia, erythema
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity, back pain
	Common	Myalgia
Reproductive system and breast disorders	Common	Gynaecomastia
General disorders and administration site conditions	Common	Pyrexia

Investigations	Common	Weight increase

The overall frequency of discontinuation in REVATIO treated patients at the recommended daily dose of 20 mg three times a day (2,9 %) was low and the same as placebo (2,9 %).

Post-marketing experience

A sudden unilateral or bilateral decrease or loss of hearing (sensorinearal deafness) with or without associated vestibular symptoms has been reported with the use of PDE5 inhibitors, including REVATIO. There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

Non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision or loss of vision, has been reported (see section 4.4).

Other side effects reported with sildenafil use not associated with PAH may include the following:

Headache, flushing, dizziness, hypotension, angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, postural hypotension, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy have also been reported.

MedDRA System organ class	**Adverse reactions**
Blood and lymphatic system disorders	Anaemia and leukopenia.
Metabolism and nutrition disorders	Thirst, oedema, gout, unstable diabetes, hyperglycaemia, peripheral oedema, hyperuricaemia, hypoglycaemic reaction and hypernatraemia.
Nervous system disorders	Ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased and hypoesthesia.
Eye disorders	Abnormal vision (Mild and transient. Predominantly colour tinge to vision, but also increased perception of light or blurred vision). Diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular oedema. Conjunctivitis, photophobia, eye haemorrhage, cataract, dry eyes

	and eye pain.
Ear and labyrinth disorders	Tinnitus, deafness, ear pain.
Respiratory, thoracic and mediastinal disorders	Nasal congestion, asthma, dyspnoea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.
Gastrointestinal disorders	Dyspepsia, vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, oesophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal haemorrhage, gingivitis.
Skin and subcutaneous tissue disorders	Urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.
Musculoskeletal and connective tissue disorders	Arthritis, arthrosis, myalgia, tendon rupture and tenosynovitis, bone pain, myasthenia, synovitis.
Renal and urinary disorders	Cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital oedema, anorgasmia and haematuria have also been reported.
Reproductive system and breast disorders	Cases of priapism and erection increased have been reported.
General disorders and administration site conditions	Face oedema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

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

5.1 Pharmacodynamic properties

Category and class: A 7.1.5 Vasodilators – peripheral

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 blood vessels including 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 phototransduction 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 mmHg 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).

Efficacy in adult patients with pulmonary arterial hypertension (PAH)

A randomised, double-blind, placebo-controlled study was conducted in 278 patients with primary PAH, PAH associated with connective tissue disease (CTD), and PAH following surgical repair of congenital heart lesions. Patients were randomised to one of four treatment groups: placebo, sildenafil 20 mg, sildenafil 40 mg, or sildenafil 80 mg, three times a day. Of the 278 patients randomised, 277 patients received at least 1 dose of study medicine. The study population consisted of 68 (25 %) men and 209 (75 %) women with a mean age of 49 years (range: 18 – 81 years) and baseline 6-minute walk test distance between 100 and 450 metres (inclusive). 175 patients (63 %) included were diagnosed with primary pulmonary hypertension, 84 (30 %) were diagnosed with PAH associated with connective tissue disease (CTD) and 18 (7 %) of the patients were diagnosed with PAH following surgical repair of congenital heart lesions. Patients across WHO functional classes I-IV participated in the study. Most patients were WHO functional Class II (107, 39 %) or III (160, 58 %); fewer patients were Class I (1, 0,4 %) or IV (9, 3 %) at baseline. Patients with left ventricular ejection fraction < 45 % or left ventricular shortening fraction < 0,2 were not studied.

Sildenafil (or placebo) was added to patients' background therapy which could have included a combination of anticoagulation, digoxin, calcium channel blockers, diuretics or oxygen. The use of

prostacyclin, prostacyclin analogues and endothelin receptor antagonists were not permitted, neither was arginine supplementation.

The primary efficacy endpoint was the change from baseline at Week 12 in 6-Minute Walk distance. The baseline Mean (SD) were 347,6 (74,8), 345,7 (90,3), 342,8 (76,7), and 337,9 (79,2) m for placebo (N=66), sildenafil 20 mg (N=67), 40 mg (N=64) and 80 mg (N=69) respectively. A statistically significant increase in 6-Minute Walk distance was observed in all 3 sildenafil dose groups compared to those on placebo. Placebo corrected increases in walk distance were 45 metres ($p < 0,0001$), 46 metres ($p < 0,0001$) and 50 metres ($p < 0,0001$) for sildenafil 20 mg, 40 mg and 80 mg respectively. There was no significant difference in effect between sildenafil doses.

The improvement in walk distance was apparent after 4 weeks of treatment and this effect was maintained at Weeks 8 and 12.

Patients on all sildenafil doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo. The baseline Mean (SD) were 53,6 (13,9), 54,5 (12,6), 48,6 (13,1), and 52,0 (16,1) mmHg for placebo (N=65), sildenafil 20 mg (N=65), 40 mg (N=63) and 80 mg (N=65) respectively. Placebo-corrected treatment effects were -2,7 mmHg ($p=0,04$), -3,0 mmHg ($p=0,01$) and -5,1 mmHg ($p < 0,0001$) for sildenafil 20 mg, 40 mg and 80 mg respectively. There was no significant difference in effect between sildenafil doses. Improvements were also seen in pulmonary vascular resistance (PVR), right atrial pressure (RAP) and cardiac output. Changes in heart rate and systemic blood pressure were negligible. The reduction in PVR was proportionally greater than the reduction in systemic vascular resistance (SVR). The incidence of clinical worsening events (in particular hospitalisations due to pulmonary arterial hypertension) showed a favourable trend in the sildenafil treatment groups. A greater percentage of patients on each of the sildenafil doses (28 %, 36 % and 42 % of subjects in sildenafil 20 mg, 40 mg and 80 mg, respectively) showed an improvement in at least 1 WHO functional class over the 12-week period compared to placebo (7 %). Improvements were also seen in quality-of-life parameters, especially in physical functioning domains, and a favourable trend was seen in Borg dyspnoea score in sildenafil-treated patients compared to placebo. The percentage of subjects who had an addition of a class of background medication was greater in the placebo group (20 %) compared to the active treatment groups (13 % on sildenafil 20 mg; 16 % on sildenafil 40 mg and 10 % on sildenafil 80 mg).

Efficacy and safety in adult patients with PAH (when used in combination with bosentan)

A randomized, double-blind, placebo-controlled study was conducted in 103 clinically stable subjects with

PAH (WHO FC II and III) who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with connective tissue disease. Patients were randomized to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62,5 – 125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil (20 mg three times a day) and placebo (13,62 m (95 % CI: -3,89 to 31,12) and 14,08 m (95 % CI: -1,78 to 29,95), respectively).

Differences in 6MWD were observed between patients with primary PAH and PAH associated with connective tissue disease. For subjects with primary PAH (67 subjects), mean changes from baseline were 26,39 m (95 % CI: 10,70 to 42,08) and 11,84 m (95 % CI: -8,83 to 32,52) for the sildenafil and placebo groups, respectively. However, for subjects with PAH associated with connective tissue disease (36 subjects) mean changes from baseline were -18,32 m (95 % CI: -65,66 to 29,02) and 17,50 m (95 % CI: -9,41 to 44,41) for the sildenafil and placebo groups, respectively.

Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see sections 4.2, 4.4 and 4.5).

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 food, the rate of absorption is reduced. In the presence of 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 % however, the extent of absorption was not significantly affected (AUC decreased by 11 %).

Distribution

The mean steady state volume of distribution (V_{ss}) 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 medicine 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 medicine. 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).

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 impairment

In volunteers with mild (CrCl (creatinine clearance) = 50 – 80 mL/min) and moderate (CrCl = 30 – 49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe (CrCl $\leq$ 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 impairment

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (85 %) and C_{max} (47 %) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh class C) 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)

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Film coat

Hypromellose

Glycerol triacetate

Lactose monohydrate

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of the container

Transparent clear PVC/aluminium blister packs of 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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