

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

REVATIO® Film-coated Tablets

COMPOSITION:

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

Contains sugar: Lactose monohydrate 0,735 mg.

Inactive excipients:

Tablet core: calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose.

Film coat: glycerol triacetate, hypromellose, lactose monohydrate, titanium dioxide (E171).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.5 Vasodilators – peripheral

PHARMACOLOGICAL ACTION:

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 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 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).

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. Of the 278 patients randomised, 277 patients received at least 1 dose of study drug. 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). Patients across WHO functional classes I-IV participated in the study. 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 was not permitted neither was arginine supplementation.

The primary efficacy endpoint was the change from baseline at Week 12 in 6-Minute Walk distance. A statistically significant increase in 6-Minute Walk distance was observed in all 3 sildenafil dose groups. 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. 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 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).

259 of the 277 treated patients entered a long-term extension study. Of these 94 % were still alive after 1 year.

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 (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 drug concentrations.

Metabolism:

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 – 45 years).

Renal insufficiency:

In volunteers with mild (CL_{cr} (creatinine clearance) = 50 – 80 ml/min) and moderate (CL_{cr} = 30 – 49 ml/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe (CL_{cr} ≤ 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.

Pre-clinical safety data:

Sildenafil shows no evidence of any mutagenic or carcinogenic potential.

INDICATIONS:

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

CONTRAINDICATIONS:

Use of REVATIO is contraindicated in patients with a known hypersensitivity to any component of the tablet.

Consistent with its known effects on the nitric oxide/cGMP pathway (see PHARMACOLOGICAL ACTION), 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. Doctors should discuss with patients the contraindication of REVATIO with concurrent organic nitrates.

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).

WARNINGS AND SPECIAL PRECAUTIONS:

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 arrhythmia within the last 6 months.
- Patients with resting hypotension (BP < 90/50) or hypertension (BP > 170/110).
- 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 CONTRAINDICATIONS).

REVATIO has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers. Physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

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. 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.

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).

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

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.

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).

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.

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 REVATIO. 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. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION.

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.

INTERACTIONS:

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 drug 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 drug interaction studies with CYP3A4 inhibitors (except more potent 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 drugs did not lead to clinically significant changes of blood pressure (supine and standing) and was well tolerated in healthy volunteers.

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 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 CONTRAINDICATIONS).

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 DOSAGE AND DIRECTIONS FOR USE). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have still greater effects (see CONTRAINDICATIONS).

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 DOSAGE AND DIRECTIONS FOR USE). 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 (ethinylloestradiol 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).

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 Pharmacodynamic properties).

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) stabilized 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 stabilized 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 a few susceptible individuals (see WARNINGS AND SPECIAL PRECAUTIONS).

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 CONTRAINDICATIONS).

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

PREGNANCY AND LACTATION:

There are no adequate data from the use of REVATIO in pregnant women. Animal studies do not

indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

It is not known whether REVATIO enters the breast milk. REVATIO should not be administered to breastfeeding mothers.

DOSAGE AND DIRECTIONS FOR USE:

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 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.

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 CONTRAINDICATIONS).

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 CONTRAINDICATIONS).

Use in children:

Safety and effectiveness of REVATIO 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 REVATIO is contraindicated (see INTERACTIONS).

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

SIDE EFFECTS:

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. 259 subjects who completed the pivotal study entered a long-term extension study. Doses up to 80 mg three times a day (4 times the recommended dose of 20 mg three times a day) were studied (N=149 patients treated for at least 1 year, 101 on 80 mg three times a day).

The most commonly reported adverse drug reactions that occurred (greater or equal to 10 %) on REVATIO than on placebo were headache, flushing, dyspepsia, back pain, diarrhoea and limb pain. 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 (> 10 %); Common (> 1 % to < 10 %).

MedDRA System Organ Class	Frequency	Adverse drug reaction
<i>Infections and infestations</i>	Common	Cellulitis, influenza, sinusitis not otherwise specified (NOS)
<i>Blood and the lymphatic system disorders</i>	Common	Anaemia NOS
<i>Metabolism and nutrition disorders</i>	Common	Fluid retention
<i>Psychiatric disorders</i>	Common	Insomnia, anxiety
<i>Nervous system disorders</i>	Very common	Headache
	Common	Migraine NOS, tremor, paraesthesia, burning sensation NOS, hypoaesthesia
<i>Eye disorders</i>	Common	Visual acuity reduced, retinal haemorrhage, visual disturbance NOS, photophobia, diplopia,

		chromatopsia, cyanopsia, abnormal sensation in eye, eye irritation
<i>Ear and labyrinth disorder</i>	Common	Vertigo
<i>Vascular disorders</i>	Very common	Flushing
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	Bronchitis NOS, epistaxis, rhinitis NOS, cough
<i>Gastrointestinal disorders</i>	Very common	Diarrhoea, dyspepsia
	Common	Gastritis NOS, gastroenteritis NOS, gastro-oesophageal reflux disease, haemorrhoids, abdominal distension
<i>Skin and subcutaneous tissue disorders</i>	Common	Alopecia, erythema
<i>Musculoskeletal, connective tissue and bone disorders</i>	Very common	Limb pain
	Common	Myalgia
<i>Reproductive system and breast disorders</i>	Common	Gynaecomastia
<i>General disorders and administration site conditions</i>	Common	Pyrexia
<i>Investigations</i>	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 %).

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 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.

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.

Ocular: 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.

Urogenital: Cases of priapism (prolonged erection) have been reported. Cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital oedema, anorgasmia and haematuria have also been reported.

Body as a whole: Face oedema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Digestive: Dyspepsia, vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal haemorrhage, gingivitis.

Haemic and lymphatic: Anaemia and leukopenia.

Metabolic and nutritional: Thirst, oedema, gout, unstable diabetes, hyperglycaemia, peripheral oedema, hyperuricemia, hypoglycaemic reaction, and hypernatremia.

Musculoskeletal: Arthritis, arthrosis, myalgia, tendon rupture, and tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: Ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, and hypoesthesia.

Respiratory: Nasal congestion, asthma, dyspnoea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and appendages: Urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special senses: Tinnitus, deafness, ear pain.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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

PRESENTATION:

Transparent clear PVC/aluminium blister packs of 90 tablets.

Opaque blue-white high-density polyethylene (HDPE) bottles with a white child-resistant closure, containing 90 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

A40/7.1.5/0131

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

Manufacturer: Fareva Amboise, Pocé-sur-Cisse, France

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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