เอกสารกำกับยา

REVATIO™

1. NAME OF THE MEDICINAL PRODUCT

Revatio™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of sildenafil (as citrate).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex film-coated tablets marked “VLE” on one side and “RVT 20” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revatio tablets are indicated for the treatment of patients with pulmonary arterial hypertension (PAH). Revatio has been shown to improve exercise ability, delay clinical worsening and to reduce mean pulmonary arterial pressure.

4.2 Posology and method of administration

Oral tablets

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.

Special populations

Elderly (≥65 years):

Dose adjustments are not required in elderly patients.

Renal impairment:

Dose adjustments are not required in patients with renal impairment.

Hepatic impairment:

Dose adjustments are not required in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). Revatio has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Pediatric population:

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

Patients using other medicinal products:

Co-administration of most potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) with sildenafil is not recommended (see section 4.5 Interactions with other medicinal products and other forms of interaction).

A downward dose adjustment to 20 mg twice a day should be considered when sildenafil is co-administered to patients already receiving CYP3A4 inhibitors like erythromycin or saquinavir. A downward dose adjustment to 20 mg once daily is recommended in case of co-administration with more potent CYP3A4 inhibitors like clarithromycin, telithromycin and nefazodone.

Dose adjustments for sildenafil may be required when co-administered with CYP3A4 inducers (see section 4.5 Interactions with other medicinal products and other forms of interaction). However, there are no data to support increasing the dose of sildenafil in combination with bosentan (see sections 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicinal products and other forms of interaction, and 5.1 Pharmacodynamic properties).

4.3 Contraindications

Co-administration with nitric oxide donors or nitrates in any form (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Vasodilatory Action

Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1 Pharmacodynamic properties). Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, for example, patients with resting hypotension (blood pressure <90/50 mmHg), patients with fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction.

Veno-occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno occlusive disease (PVOD). 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. Should signs of pulmonary edema occur when Revatio is administered, consider the possibility of associated PVOD.

Cardiovascular Risk Factors

As there are no controlled clinical data on the safety or efficacy of Revatio in the following groups, prescribe with caution for:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP >170/110);
- Patients currently on bosentan therapy.

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage and transient ischemic attack have been reported post-marketing in temporal association with the use of sildenafil for erectile dysfunction. 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.

Alpha-blockers

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5 Interactions with other medicinal products and other forms of interaction). In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.

Visual Events

Non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision or loss of vision, has been reported rarely post-marketing with the use of all phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most of these patients had risk factors, such as low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 males aged $\geq$50 per year in the general population. In case of sudden visual loss, patients should be advised to stop taking sildenafil and consult a physician immediately.

Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, physicians should discuss this risk with these patients and whether they could be adversely affected by use of PDE5 inhibitors. PDE5 inhibitors, including sildenafil should be used with caution in these patients and only when the anticipated benefits outweigh the risks.

Retinitis Pigmentosa

The safety of sildenafil has not been studied in patients with known hereditary degenerative retinal disorders, such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases), therefore, Revatio should be administered with caution to these patients.

Bleeding Disorders

Studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, sildenafil should be administered with caution to these patients.

Vitamin K Antagonists

The incidence of epistaxis was higher in patients with PAH secondary to connective tissue disease (CTD) (sildenafil 12.9%, placebo 0%) than in primary pulmonary hypertension patients (sildenafil 3.0%, placebo 2.4%) and was higher in sildenafil-treated patients treated with concomitant oral vitamin K antagonist (8.8% versus 1.7% not treated with concomitant vitamin K antagonist).

Priapism

Sildenafil 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 anemia, multiple myeloma or leukemia).

Prolonged erections and priapism have been reported with sildenafil 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 (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Hearing Impairment

Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing, patients should be advised to consult a physician promptly.

Use of Sildenafil with Bosentan

In a study of PAH patients (primary PAH and secondary PAH associated with CTD) on background bosentan therapy, no incremental benefit (6-minute walk distance (6MWD)) of sildenafil co-administered with bosentan was demonstrated over bosentan alone. The results of the 6MWD were different between primary PAH and PAH associated with CTD. The mean result

of the combination of sildenafil and bosentan was numerically worse than bosentan alone in patients with PAH associated with CTD but numerically better than bosentan alone in patients with primary PAH. Therefore, healthcare professionals should use their medical judgment to assess the clinical response when sildenafil is co-administered with bosentan in primary PAH. The combined use of sildenafil and bosentan in patients with PAH associated with CTD is not recommended (see section 5.1 Pharmacodynamic properties).

Use with Ritonavir and Other Potent CYP3A Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A4 inhibitors with REVATIO is not recommended (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Concomitant Use with Other PDE5 Inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitor products, including VIAGRA®, has not been studied in PAH patients and such concomitant use is not recommended. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitor products.

4.5 Interactions with other medicinal products and other forms of interaction

Unless otherwise specified, drug interaction studies have been performed in healthy adult male subjects using oral sildenafil. These results are relevant to other populations and routes of administration.

Effects of Other Medicinal Products 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.

***In vivo* studies:**

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} (see section 4.2 Posology and

method of administration). 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.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent CYP3A4 inhibitor, at steady-state (500 mg twice a day) 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 cytochrome P450 substrates. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not recommended (see section 4.2 Posology and method of administration).

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 Posology and method of administration. The most potent CYP3A4 inhibitors, such as ketoconazole and itraconazole would be expected to have effects similar to those of ritonavir (see section 4.2 Posology and method of administration).

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady-state (500 mg twice a day for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). For dose recommendations see section 4.2 Posology and method of administration.

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 these CYP3A4 inhibitors (see section 4.2 Posology and method of administration).

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.

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.

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

Concomitant administration of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil.

Population Pharmacokinetic Analyses

CYP3A4 inhibitors and beta-blockers

A population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 30% reduction in sildenafil clearance when sildenafil was co-administered with mild/moderate CYP3A4 inhibitors and an approximately 34% reductions in sildenafil clearance when co-administered with beta-blockers. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg three times a day compared to its exposure at a dose of 20 mg three times a day. This concentration range covers the increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A4 inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir).

CYP3A4 inducers

A population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 3-fold increase in sildenafil clearance when sildenafil was co-administered with mild CYP3A4 inducers, which is consistent with the effect of bosentan on sildenafil clearance in healthy volunteers. Concomitant administration of potent CYP3A4 inducers is expected to cause substantial decreases in plasma levels of sildenafil.

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 Posology and method of administration, 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Effects of Sildenafil on Other Medicinal Products

***In vitro* studies:**

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} >150 μM). Sildenafil is not expected to affect the pharmacokinetics of compounds which are substrates of these CYP enzymes at clinically relevant concentrations.

***In vivo* studies:**

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1 Pharmacodynamic properties), 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 Contraindications).

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 lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see section 4.4 Special warnings and precautions for use).

In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional mean maximum reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional mean maximum 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 (see section 5.1 Pharmacodynamic properties).

No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

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 0.08% (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 a day) (see section 4.2 Posology and method of administration).

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 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 Posology and method of administration and 5.1 Pharmacodynamic properties).

Sildenafil (100 mg single dose) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

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

Pediatric 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 in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryo/fetal development. Studies in animals have shown toxicity with respect to post-natal development (see section 5.3 Preclinical safety data).

Due to lack of data, Revatio should not be used in pregnant women unless strictly necessary.

Breast-feeding

There are no adequate and well-controlled studies in lactating women. Limited data indicate that sildenafil and its active metabolite are excreted into breast milk at very low levels. Amounts ingested by the breastfed infant would not be expected to cause any adverse effects. Prescribers should carefully assess the mother's clinical need for Revatio and any potential adverse effects on the breastfed child.

Fertility

Non-clinical data revealed no special hazard for humans based on conventional studies of fertility (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they might be affected by Revatio, before driving or operating machinery. The effect of sildenafil on the ability to drive and use machinery has not been studied.

4.8 Undesirable effects

Clinical Data

In the pivotal placebo-controlled study of Revatio in PAH, 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. The overall frequency of discontinuation in sildenafil 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%). The 259 subjects who completed the pivotal study entered a long-term extension study. Doses up to 80 mg three times a day were studied and after 3 years 87% of 183 patients on treatment were receiving Revatio 80 mg three times a day.

In a placebo-controlled study of Revatio as an adjunct to intravenous epoprostenol in PAH, a total of 134 patients were treated with Revatio at daily doses ranging from 20 mg to 80 mg three times a day and epoprostenol, and 131 patients were treated with placebo and epoprostenol. The duration of treatment was 16 weeks. The overall frequency of discontinuations in sildenafil/epoprostenol treated patients due to adverse events was 5.2% compared to 10.7% in the placebo/epoprostenol treated patients. There were 242 subjects who completed the initial study and entered a long-term extension study. Doses up to 80 mg three times a day (4 times the maximum recommended dose of 20 mg three times a day) were studied and after 3 years 68% of 133 patients on treatment were receiving Revatio 80 mg three times a day.

The most commonly reported adverse reactions that occurred (≥10%) in the Revatio combined data set compared to placebo were headache, flushing, dyspepsia, diarrhoea and pain in extremity.

Adverse reactions that were reported in ≥3% of Revatio-treated patients and were more frequent (>1% difference) on Revatio in the pivotal study or in the Revatio combined data set of the two placebo-controlled studies in PAH, at doses of 20, 40 or 80 mg three times a day are shown in Table 1.

Table 1: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC. Adult Patients - Adverse Drug Reactions reported in ≥3% of Revatio-treated patients, and more frequent (>1% difference) in patients on Revatio in the pivotal study or in the Revatio combined data set of the two placebo-controlled studies in PAH (at doses of 20, 40 or 80 mg three times a day):

MedDRA System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**
Infections and infestations		influenza
Psychiatric disorders		insomnia
Nervous system disorders	headache	
Eye disorders		visual disturbance[a], vision blurred
Vascular disorders	flushing	
Respiratory, thoracic and mediastinal disorders		epistaxis, cough[a], nasal congestion
Gastrointestinal disorders	diarrhoea, dyspepsia	
Musculoskeletal and connective tissue disorders	pain in extremity	myalgia, back pain
General disorders and administration site conditions		pyrexia[a]

[a] Visual disturbance, Cough and Pyrexia did meet the stated criteria in A1481140, and based on clinical judgment they have been included even though in the combined data set of A1481140 and A1481141, they did

not meet the same criteria.

In a study to assess the effects of different dose levels of sildenafil on mortality in adults with PAH, the group who received the lower dose 5 mg three times a day (4 times lower than the recommended dose) showed a higher observed number of deaths (all related to underlying disease/disease under study), serious adverse events and severe adverse events than the 20 mg three times a day (recommended dose) and 80 mg three times a day (4 times the maximum recommended dose) groups (see section 5.1).

Overall, the safety data for sildenafil 20 mg three times a day (recommended dose) and for the higher dose, sildenafil 80 mg three times a day (4 times the maximum recommended dose), were consistent with the established safety profile of sildenafil in previous adult PAH studies. The most commonly reported adverse reactions that occurred (≥ 5%) in the Revatio combined data set were headache and dizziness.

Post-marketing Experience:

In the post-marketing experience these additional adverse reactions were reported with Revatio:

Reproductive system and breast disorders: priapism, erection increased (frequency not known).

4.9 Overdose

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.

In cases of overdose, standard 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

Sildenafil is a potent and selective inhibitor of cGMP specific PDE5 the enzyme that is responsible for degradation of cGMP. Apart from the presence of this enzyme in the corpus cavernosum of the penis, PDE5 is also present in the pulmonary vasculature. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with PAH this can lead to 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. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity 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 PAH 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 PAH no clinically relevant effects on the ECG were reported.

In a study of the hemodynamic 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 color discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in color discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity, contrast sensitivity, electroretinograms, intraocular pressure, or pupillometry. 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, color discrimination simulated traffic light, Humphrey perimeter and photostress).

Efficacy in Adult Patients with PAH

A randomized, double blind, placebo-controlled study was conducted in 278 patients with primary PAH, PAH associated with CTD, and PAH following surgical repair of congenital heart lesions. Patients were randomized 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 randomized, 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 (6MWD) between 100 and 450 meters (mean: 344 meters). 175 patients (63%) included were diagnosed with primary pulmonary hypertension, 84 (30%) were diagnosed with PAH associated with CTD and 18 (7%) of the patients were diagnosed with PAH following surgical repair of congenital heart lesions. 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 anticoagulants, digoxin, calcium channel blockers, diuretics and/or oxygen. The use of prostacyclin, prostacyclin analogues and endothelin receptor antagonists was not permitted neither was arginine supplementation. Patients who previously failed bosentan therapy were excluded from the study.

The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. A statistically significant increase in 6MWD was observed in all 3 sildenafil dose groups compared to those on placebo. Placebo corrected increases in walk distance were 45 meters ($p < 0.0001$), 46 meters ($p < 0.0001$) and 50 meters ($p < 0.0001$) 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. Mean treatment effects consistently showed improvement in 6MWD in all sildenafil groups compared to placebo in all pre-defined subpopulations based on demographics, geographical regions, disease characteristics (in particular effects were similar among WHO functional class groups and etiologies) and baseline parameters (walk test and hemodynamics).

When analyzed by WHO functional class, a statistically significant increase in 6MWD was observed in the 20 mg dose group. For class II and class III, placebo corrected increases of 49 meters ($p = 0.0007$) and 45 meters ($p = 0.0031$) were observed, respectively.

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. 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 hospitalizations due to PAH) showed a favorable 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 favorable trend was seen Borg dyspnea 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).

Long-term Survival Data

Patients enrolled into the pivotal study were eligible to enter a long-term open label extension study. A total of 207 patients were treated with Revatio in the pivotal study, and their long-term survival status was assessed for a minimum of 3 years. In this population, Kaplan-Meier estimates of 1, 2 and 3 year survival were 96%, 91% and 82%, respectively. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 99%, 91%, and 84%, respectively, and for patients of WHO functional class III at baseline was 94%, 90%, and 81%, respectively.

Efficacy in Adult Patients with PAH (when used in combination with epoprostenol)

A randomized, double-blind, placebo-controlled, study was conducted in 267 patients with PAH who were stabilized on intravenous epoprostenol. The PAH patients included those with Primary PAH, and PAH associated with CTD. Patients were randomized to placebo or sildenafil (in a fixed titration starting from 20 mg to 40 mg and then 80 mg, three times a day) when used in combination with intravenous epoprostenol. The primary efficacy endpoint was the change from baseline at Week 16 in 6MWD. There was a statistically significant benefit of sildenafil compared to placebo in 6MWD. The mean change from baseline at Week 16 was 30.1 m for the sildenafil group compared with 4.1 m for the placebo group, giving an adjusted treatment difference of 26.0 m (95% CI: 10.8, 41.2) (p = 0.0009). Patients on sildenafil achieved a statistically significant reduction in mean Pulmonary Arterial Pressure (mPAP) compared to those on placebo. A mean placebo-corrected treatment effect of -3.9 mmHg was observed in favor of sildenafil (95% CI: -5.7, -2.1) (p = 0.00003).

Delay in Clinical Worsening

Treatment with sildenafil significantly delayed the time to clinical worsening of PAH compared to placebo (p = 0.0074) with Kaplan-Meier (K-M) estimates demonstrating that placebo patients were 3 times more likely to experience an event (see Table 2). Time to clinical worsening was defined as the time from randomization to the first occurrence of a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy). 23 subjects experienced clinical worsening events in the placebo group (17.6%) compared with 8 subjects in the sildenafil group (6.0%).

Table 2: Clinical Worsening		
	Placebo (N = 131)	**Revatio** (N = 134)
Number of subjects with clinical worsening event n (%)	23 (17.6)	8 (6.0)
Proportion worsened (K-M estimates) 95% Confidence intervals	0.187 (0.12 - 0.26)	0.062 (0.02 - 0.10)

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 subjects with PAH who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with CTD. 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 and placebo (13.62 m and 14.08 m, respectively).

Differences in 6MWD were observed between patients with primary PAH and PAH associated with CTD. For subjects with primary PAH (67 subjects), mean changes from baseline were 26.39 m and 11.84 m for the sildenafil and placebo groups, respectively. However, for subjects with PAH associated with CTD (36 subjects) mean changes from baseline were -18.32 m and 17.50 m for the sildenafil and placebo groups, respectively.

Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan versus bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicinal products and other forms of interaction).

Effects on mortality in adults with PAH

A study to assess the effects of different dose levels of sildenafil on mortality in adults with PAH was conducted following the observation of a higher risk of mortality in pediatric patients taking a high dose of sildenafil three times a day, based on body weight, compared to those taking a lower dose in the long-term extension of the pediatric clinical trial.

The study was a randomized, double-blind, parallel-group study in 385 adults with PAH. Patients were randomly assigned 1:1:1 to one of three treatment groups (5 mg three times a day (4 times lower than the recommended dose), 20 mg three times a day (recommended dose) and 80 mg three times a day (4 times the maximum recommended dose). In total, the majority of patients were PAH treatment naïve (83.4%). For most patients the etiology of PAH was idiopathic (71.7%). The most common WHO Functional Class was Class III (57.7% of patients). All three treatment groups were well balanced with respect to baseline demographics of strata history of PAH treatment and etiology of PAH, as well as the WHO Functional Class categories.

The primary objective of the study was to test for the non-inferiority of sildenafil 80 mg three times a day versus 5 mg three times a day for mortality; mortality rate with the 80 mg three times a day dose was no worse than double the mortality rate for the 5 mg three times a day dose. The primary efficacy endpoint was time to death (mortality).

The key secondary efficacy endpoint was time to first event (clinical worsening). Clinical worsening for the purpose of this study was defined as a composite endpoint of all-cause mortality, hospitalization for worsening PAH or disease progression. An additional secondary endpoint was 6MWD at Months 6 and 12.

Overall survival:

At the time of a planned interim analysis (50% deaths) it was identified that the primary efficacy objective of this protocol was met and therefore the study was stopped. Based on the primary efficacy endpoint (mortality), the non-inferiority of sildenafil 80 mg three times a day arm versus 5 mg three times a day arm was met using a 2-sided significance level of 0.003 for the interim analysis. Primary comparison of the 80 mg three times a day group to the 5 mg three times a day group yielded the HR (99.7% CI)=0.51 (0.22, 1.21) (see Table 4) i.e. Non-inferiority was met.

The mortality rate with the high dose sildenafil 80 mg three times a day dose was no worse than double the mortality rate for the low dose 5 mg three times a day dose in the treatment of adults with PAH.

Table 4. Hazard Ratios for Overall Survival, Assessed in the Proportional Hazards Model – Intent To Treat Population

	Sildenafil 5 mg N=129	Sildenafil 20 mg N=128	Sildenafil 80 mg N=128
Patient-years of follow-up	329.8	340.5	356.7
Number of deaths (%)	34 (26.4)	25 (19.5)	19 (14.8)
On treatment deaths[a] (%)	22 (17.1)	13 (10.2)	15 (11.7)
Off treatment deaths (%)	12 (9.3)	12 (9.4)	4 (3.1)
Hazard ratio relative to sildenafil 5 mg			
Hazard ratio estimate[b]		0.68	0.51
99.7% CI		0.31, 1.49	0.22, 1.21
Hazard ratio relative to sildenafil 20 mg			
Hazard ratio estimate[b]			0.74
99.7% CI			0.30, 1.84

[a] On treatment deaths: Any death within 7 days of last dose was regarded as “On treatment”, thus might include deaths occurred after discontinuation from study treatment.

[b] Hazard ratio estimates from the proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Clinical worsening:

The time to first event of clinical worsening for the comparison of the 80 mg three times a day group to the 5 mg three times a day group yielded the HR (99.7% CI) = 0.44 (0.22, 0.89) (see Table 5). The p-value for testing of the superiority of 80 mg three times a day group compared to 5 mg three times a day group regarding clinical worsening was $p < 0.001$ (see Table 5) which is evidence (relative to a significance level of 0.003) of the superiority of 80 mg three times a day group compared to 5 mg three times a day group regarding clinical worsening.

Table 5. Hazard Ratios for Time to First Event of Clinical Worsening – Intent To Treat Population

	Sildenafil 5 mg N=129	Sildenafil 20 mg N=128	Sildenafil 80 mg N=128
Patient-years of follow-up	249.6	276.4	306.5

Table 5. Hazard Ratios for Time to First Event of Clinical Worsening – Intent To Treat Population

	Sildenafil 5 mg N=129	Sildenafil 20 mg N=128	Sildenafil 80 mg N=128
Number of patients with clinical worsening	52	36	28
First Event of clinical worsening[a] n (%)			
Disease progression[b]	8 (6.2)	2 (1.6)	6 (4.7)
Hospitalization for PAH[c]	28 (21.7)	23 (18.0)	11 (8.6)
Death[d]	16 (12.4)	11 (8.6)	11 (8.6)
Hazard ratio relative to sildenafil 5 mg			
Hazard ratio estimate[e]		0.63	0.44
99.7% CI		0.33, 1.21	0.22, 0.89
p-value		0.035	<0.001
Hazard ratio relative to sildenafil 20 mg			
Hazard ratio estimate[e]			0.72
99.7% CI			0.34, 1.52
p-value			0.195

Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; PAH = pulmonary arterial hypertension.

a. Clinical worsening events were defined as reduction from baseline in the 6MWD test by at least 15% and worsening functional class from baseline, both confirmed by a second test/evaluation within 2 weeks.

b. Count of cases of disease progression as the first event of clinical worsening.

c. Count of non-elective hospital stays for worsening PAH as the first event of clinical worsening.

d. Count of deaths as the first event of clinical worsening.

e. Hazard ratio estimates from the proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH. P-value from the Wald test.

6MWD at Months 6 and 12:

At baseline, the median of 6MWD for the Intent To Treat (ITT) population was 342.0 m, 331.8 m, and 352.0 m in patients of the sildenafil 5 mg three times a day, sildenafil 20 mg three times a day, and sildenafil 80 mg three times a day groups, respectively. At Month 6, the median change from baseline was highest for sildenafil 80 mg three times a day with 27.8 m compared to 17.5 m

and 19.3 m for sildenafil 5 mg three times a day and sildenafil 20 mg three times a day groups, respectively. The same was seen at Month 12, the median change from baseline for sildenafil 80 mg three times a day group was 33.0 m compared to 17.0 m for sildenafil 5 mg three times a day and 30.5 m in sildenafil 20 mg three times a day groups.

Overall, the safety data for sildenafil 20 mg three times a day (recommended dose) and for the higher dose sildenafil 80 mg three times a day dose (4 times the maximum recommended dose) were consistent with the established safety profile of sildenafil in previous adult PAH studies however, at higher doses adverse reactions were of greater severity and were reported more frequently.

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 41% (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 a 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 there was 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. Sildenafil and its major circulating N-desmethyl metabolite are approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.0002% (average 188 ng) of the administered dose may appear in the semen of patients.

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 phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolized, with a terminal half-life of approximately 4 h. In patients with PAH, however, the ratio of UK-103,320 to sildenafil is higher. 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 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (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, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal impairment:

In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. In volunteers with severe renal impairment (creatinine clearance <30 mL/min), sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100% and 88%, respectively, compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased by 200% and 79%, respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic impairment:

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh class 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 PAH 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 PAH.

In patients with PAH, 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 PAH compared to healthy volunteers.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity potential, and toxicity to reproduction.

In pups of rats which were pre- and postnatally treated with 60 mg/kg sildenafil, a decreased litter size, a lower pup weight on day 1 and a decreased 4-day survival were seen at exposures which were approximately fifty times the expected human exposure at 20 mg three times a day. Effects in non-clinical studies were observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Please see details on carton.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

7. MARKETING AUTHORISATION HOLDER

Viatris (Thailand) Limited

Warnings (based on the Ministry of Public Health Announcement)

Use for patients diagnosed with pulmonary artery hypertension only.