PT. PFIZER INDONESIA
Local Product Document

Generic Name: Sildenafil Citrate
Trade Name: Revatio
CDS Effective Date: May 23, 2017
Supersedes: NA

1. NAME OF THE MEDICINAL PRODUCT

1.1. Product Name

Revatio

1.2. Strength

10 mg/mL

1.3. Pharmaceutical Dosage Form

White to off-white powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative Declaration

After reconstitution, each mL of the oral suspension contains 10 mg of sildenafil (as citrate). Following reconstitution, the volume of suspension is 112 mL containing 1.12 g of sildenafil (as citrate), providing a usable volume of 90 mL of suspension at a sildenafil concentration of 10 mg/mL, adequate to provide a 30 day supply of a 10 mg dose, or a 15 day supply of a 20 mg dose.

2.2. Quantitative Declaration

Each mL of oral suspension contains 250 mg sorbitol. For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white powder. Once reconstituted, white to off-white opaque fluid containing undissolved solids.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Pediatric Population

Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

4.2. Posology and method of administration

Posology:

Pediatric population (1 year to 17 years)

For pediatric patients aged 1 year to 17 years old, the recommended dose in patients ≤20 kg is 10 mg (1 mL of compounded suspension) three times a day and for patients >20 kg is 20 mg (2 mL of compounded suspension) three times a day. Higher than recommended doses should not be used in pediatric patients with PAH (see also sections 4.4 and 5.1).

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).

A downward dose adjustment to 20 mg (10 mg if by intravenous injection) 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 (10 mg if by intravenous injection) 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). However, there are no data to support increasing the dose of sildenafil in combination with bosentan (see sections 4.4, 4.5, and 5.1).

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
The safety and efficacy of Revatio in pediatric PAH have been evaluated in patients aged 1 to 17 years.

The most frequent adverse reactions were consistent with those described in adults. The benefit-risk has not been established in pediatric patients <1 year of age.

Method of administration
Revatio powder for oral suspension is for oral use only. The reconstituted oral suspension (a white, grape flavored suspension) should be taken approximately 6 to 8 hours apart with or without food.

Before withdrawing the required dose, shake the bottle vigorously for a minimum of 10 seconds.

For instructions on reconstitution of the medicinal product before administration (see section 6.6).

4.3. Contraindications
Co-administration with nitric oxide donors or nitrates in any form (see section 4.5).

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.

Combination with the most potent of the CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir).

Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated:
Severe hepatic impairment,
Recent history of stroke or myocardial infarction,
Severe hypotension (blood pressure < 90/50 mmHg) at initiation.

4.4. Special warnings and precautions for use
No clinical data are available for sildenafil intravenous administration in patients who are clinically or hemodynamically unstable. Its use is accordingly not recommended in these patients.

In the long term pediatric extension study, an increase in deaths was observed in patients administered doses higher than the recommended dose. Therefore, doses higher than the recommended doses should not be used in pediatric patients with PAH.

<u>Vasodilatory action</u>
Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). 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.

<u>Cardiovascular risk factors</u>
Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension and hypotension have been reported postmarketing 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.

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 ≥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.

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). 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.

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.

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) and therefore its use is not recommended.

Bleeding disorders
Studies with human platelets indicate that sildenafil potentiates the antiaggregatory 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.

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 is not treated immediately, penile tissue damage and permanent loss of potency could result.

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).

Hearing impairment
Sudden decrease or loss of hearing has been reported in a small number of postmarketing 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).

Concomitant use with other PDE5 inhibitors

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.

4.5. Interaction with other medicinal products and other forms of interactions
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 intravenous sildenafil
Predictions based on a pharmacokinetic model suggest that drug-drug interactions with CYP3A4 inhibitors should be less than observed after oral sildenafil administration. The magnitude of the interaction is expected to be reduced for intravenous sildenafil, as interactions for oral sildenafil are due, at least in part, to effects on oral first pass metabolism.

Effects of other medicinal products on oral 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). 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.

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

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).

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. 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).

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.

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).

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.

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

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

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.

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

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, 4.4 and 5.1).

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), 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).

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).

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).

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

No interactions were observed between sildenafil (100 mg single dose) and acenocoumarol.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

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

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 and 5.1).

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.

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

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. Pregnancy and lactation
Women of childbearing potential and contraception in males and females
Due to lack of data on effects of Revatio in pregnant women, Revatio is not recommended for women of childbearing potential unless also using appropriate contraceptive measures.

Pregnancy
There are no data from the use of sildenafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, and embryo/fetal development. Studies in animals have shown toxicity with respect to postnatal development (see section 5.3).

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).

4.7. Effects on ability to drive and use machine
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
Oral
In the pivotal placebo controlled study of Revatio in PAH, a total of 207 patients were randomized to and treated with 20 mg, 40 mg, or 80 mg TID doses of Revatio and 70 patients were randomized to placebo. The duration of treatment was 12 weeks. The overall frequency of discontinuation in sildenafil treated patients at doses of 20 mg, 40 mg and 80 mg TID was 2.9%, 3.0%, and 8.5% respectively, compared to 2.9 % with placebo. Of the 277 subjects treated in the pivotal study, 259 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 administered and after 3 years 87% of 183 patients on treatment were receiving Revatio 80 mg TID.

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. Newly reported adverse reactions, which occurred more frequently in the sildenafil/epoprostenol group, were ocular hyperaemia, vision blurred, nasal congestion, night sweats, back pain and dry mouth. 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 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. 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	**Adverse Drug Reactions**
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	myalgia, back pain, pain in extremity
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.

Solution for Injection

Study A1481262 was a single center, open label study to assess the safety, tolerability and pharmacokinetics of a single intravenous dose of sildenafil (10 mg) administered as a bolus injection to patients with PAH who were stable on oral Revatio 20 mg three times a day.

A total of 10 PAH subjects enrolled and completed the study. The mean postural changes in systolic and diastolic blood pressure over time were small (<10 mmHg) and returned towards baseline beyond 2 hours. No symptoms of hypotension were associated with these changes. The mean changes in heart rate were clinically insignificant. Two subjects experienced a total of 3 adverse reactions (flushing, flatulence and hot flush). There was one serious adverse event in a subject with severe ischemic cardiomyopathy who experienced ventricular fibrillation and death 6 days post study drug; the event was judged to be unrelated to study drug.

Clinical Trials Experience (Pediatric Patients)

Revatio has been studied in a total of 234 PAH pediatric subjects 1 through 17 years of age in a 16-week, double-blind placebo-controlled study. Of these subjects, 220 patients continued in a long-term extension study. Long term survival status has been assessed for a minimum of 3 years.

The adverse reactions profile seen in this pediatric study was consistent with that in adults. A total of 174 patients were treated with Revatio in the initial 16-week study and 60 patients received placebo.

The most frequently reported adverse drug reactions in the sildenafil treatment groups, reported with greater frequency than placebo (>2%), are shown in Table 2.

Table 2. Revatio Adverse Drug Reactions in >3% of Patients (in any Active Group) and More Frequent (>2%) than Placebo

MedDRA System Organ Class	**Adverse Drug Reactions**
Infections and infestations	pneumonia, URTI, bronchitis, pharyngitis
Respiratory, thoracic and mediastinal disorders	rhinorrhea
Gastrointestinal disorders	vomiting, nausea
Reproductive system and breast disorders	erection increased
General disorders and administration site conditions	pyrexia

URTI = upper respiratory tract infection

The overall frequency of discontinuation in Revatio-treated patients was 2.3% and was similar to the placebo group.

Of the 234 pediatric subjects treated in the short-term, placebo-controlled study, 220 subjects entered the long-term extension study. Subjects on active sildenafil therapy continued on the same treatment regimen, while those in the placebo group in the short-term study were randomly reassigned to sildenafil treatment; subjects ≤20 kg of body weight entered the medium or high dose groups, while subjects weighing >20 kg entered the low, medium or high dose groups. Of the total 229 subjects who received sildenafil, there were 55, 74, and 100 subjects in the low, medium and high dose groups, respectively. Median duration of sildenafil treatment was 1696 days.

The most common adverse reactions reported across the duration of the short-term and long-term studies were generally similar to those observed in the short-term study. Adverse reactions reported in >10% of 229 subjects treated with sildenafil (combined dose group) were upper respiratory infection (31%), headache (26%), vomiting (22%), bronchitis (20%), pharyngitis (18%), pyrexia (17%), diarrhoea (15%), and influenza, epistaxis (12% each). Most of these adverse reactions were considered mild to moderate in severity.

Serious adverse events were reported in 94 (41%) of the 229 subjects receiving sildenafil. Of the 94 subjects reporting a serious adverse event, 14/55 (25.5%) subjects were in the low dose group, 35/74 (47.3%) in the medium dose group, and 45/100 (45%) in the high dose group. The most common serious adverse events that occurred with a frequency ≥ 1 % in sildenafil patients (combined doses) were pneumonia (7.4%), cardiac failure, pulmonary hypertension (each 5.2%), upper respiratory tract infection (3.1%), right ventricular failure, gastroenteritis (each 2.6%), syncope, bronchitis, bronchopneumonia, pulmonary arterial hypertension (each 2.2%), chest pain, dental caries (each 1.7%), and cardiogenic shock, gastroenteritis viral, urinary tract infection (each 1.3%).

The following serious adverse events were considered to be treatment related, enterocolitis, convulsion, hypersensitivity, stridor, hypoxia, neurosensory deafness and ventricular arrhythmia.

During the conduct of the study, there were a total of 42 deaths reported. 37 deaths occurred prior to a decision to down titrate subjects to a lower dosage, based on an observed mortality imbalance with increasing sildenafil doses. Among these 37 deaths, the number (%) of deaths was 5/55 (9.1%), 10/74 (13.5%), and 22/100 (22%) in the sildenafil low, medium, and high dose groups, respectively. An additional 5 deaths (3 in the medium dose group, and 2 in the high dose group) were reported subsequently. The causes of deaths were typical of patients with PAH. Higher than recommended doses should not be used in pediatric patients with PAH (see sections 4.2, 4.4 and 5.1).

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. At single doses of 200 mg the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, and altered vision) was 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 mm Hg 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 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 3). 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 3: 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 vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see sections 4.2, 4.4, 4.5).

Pediatric population

A total of 234 subjects aged 1 to 17 years were treated in a randomized, double-blind, multi-center, placebo-controlled parallel-group, dose-ranging study. Subjects (38% male and 62% female) had a body weight ≥8 kg, and had primary pulmonary hypertension (PPH) [33%], or PAH secondary to congenital heart disease [systemic-to-pulmonary shunt 37%, surgical repair 30%]. In this trial, 63 of 234 (27%) patients were <7 years old (sildenafil low dose = 2; medium dose = 17; high dose = 28; placebo = 16) and 171 of 234 (73%) patients were 7 years or older (sildenafil low dose = 40; medium dose = 38; and high dose = 49; placebo = 44). Most subjects were WHO Functional Class I (75/234, 32%) or II (120/234, 51%) at baseline; fewer patients were Class III (35/234, 15%) or IV (1/234, 0.4%); for a few patients (3/234, 1.3%), the WHO Functional Class was unknown.

Patients were naïve for specific PAH therapy and the use of prostacyclin, prostacyclin analogues and endothelin receptor antagonists was not permitted in the study, and neither was arginine supplementation, nitrates, alpha-blockers and potent CYP450 3A4 inhibitors.

The primary objective of the study was to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects to improve exercise capacity as measured by the Cardiopulmonary Exercise Test (CPET) in subjects who were developmentally able to perform the test, n = 115). Secondary endpoints included hemodynamic monitoring, symptom assessment, WHO functional class, change in background treatment, and quality of life measurements.

Patients were allocated to one of three sildenafil treatment groups (low, medium or high) or placebo. Actual doses administered were dependent on body weight (see Table 4).

Table 4. Treatment Allocation by Dose and Body Weight in Pediatric Study

	Placebo	Low Dose		Medium Dose		High Dose	
Body Weight(kg)	N	Dose	N	Dose	N	Dose	N
≥8 - 20	18		na	10 mg	15	20 mg	35
>20 - 45	32	10 mg	31	20 mg	30	40 mg	31
>45	10	10 mg	11	40 mg	10	80 mg	11

The proportion of subjects receiving supportive medicinal products at baseline (anticoagulants, digoxin, calcium channel blockers, diuretics and/or oxygen) was similar in the combined sildenafil treatment group (47.7%) and the placebo treatment group (41.7%).

The primary endpoint was a percentage change in VO_{2peak} from baseline to Week 16 assessed by CPET. Mean baseline peak volume of oxygen consumed (VO_2) values were comparable across the sildenafil treatment groups (17.37 to 18.03 mL/kg/min), and slightly higher for the placebo treatment group (20.02 mL/kg/min). See Figure 1 and Table 5. A total of 106 out of 234 (45%) subjects were evaluable for CPET, which comprised those children ≥ 7 years old and developmentally able to perform the test. Children <7 years (sildenafil combined dose = 47; placebo = 16) were evaluable only for the secondary endpoints.

Mean increases in VO_{2peak} percentage change from baseline at Week 16, were observed with all 3 sildenafil doses (range of 6.44% – 13.40%, Figure 1), with little change with placebo (0.53%). The estimated difference between the combined sildenafil doses and placebo was 7.71% (95% CI: -0.19 to 15.60). See Table 5.

Figure 1. % Change from Baseline in VO_{2Peak}: Mean (95% Confidence Intervals)

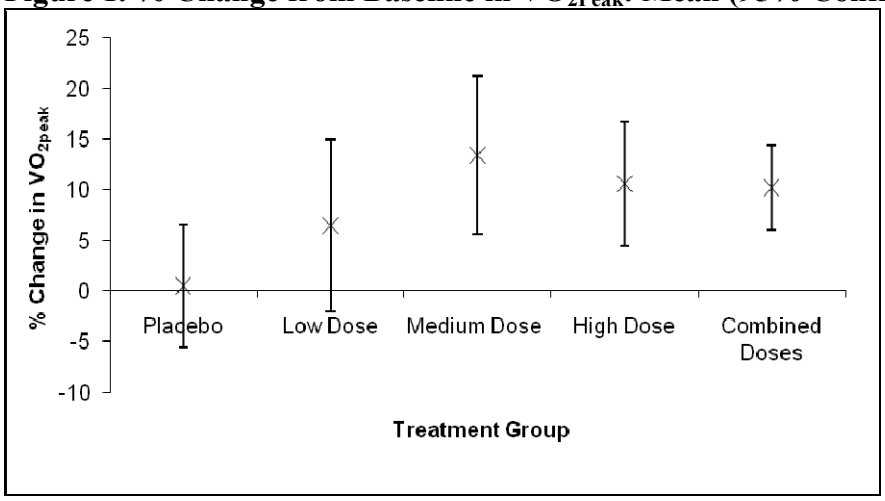

Table 5. Placebo Corrected % Change from Baseline in VO_{2peak} by Active Treatment Group

Treatment Group	Estimated Difference	95% Confidence Interval
Low Dose (n=24)	3.81	-6.11, 13.73
Medium Dose (n=26)	11.33	1.72, 20.94
High Dose (n=27)	7.98	-1.64, 17.60
Combined Dose Groups (n=77)	7.71 (p = 0.056)	-0.19, 15.60

Note: n=29 for placebo group

Estimates based on ANCOVA with adjustments for the covariates baseline VO_{2peak}, etiology and weight group

Patients on sildenafil experienced dose dependent reductions in PVRI and mPAP compared to those on placebo (see Table 6).

Table 6. Placebo Corrected Changes in Hemodynamic Parameters by Dose Group

PARAMETER [Estimate (95% CI)]	Low Dose	Medium Dose	High Dose
PVRI (%)	-2% (-20%, 20%) n=37	-18% (-32%, -2%) n=51	-27% (-39%, -14%) n=68
mPAP (mmHg)	1.6 (-4.5, 7.6) n=39	-3.5 (-8.9, 1.9) n=55	-7.3 (-12.4, -2.1) n=71
CI (%)	10% (-4%, 26%) n=37	4% (-7%, 18%) n=51	15% (3%, 29%) n=69
SVRI (%)	-9% (-22%, 7%) n=37	-5% (-17%, 10%) n=50	-16% (-26%, -4%) n=68
RAP (mmHg)	-0.17 (-1.91, 1.57) n=39	-0.19 (-1.73, 1.36) n=55	-1.14 (-2.61, 0.33) n=71
HR (%)	3% (-5%, 12%) n=39	2% (-5%, 9%) n=55	-2% (-9%, 5%) n=71

Note: n= 52, 56, 55, 54, 56, and 56 placebo subjects for PVRI, mPAP, CI, SVRI, RAP, and HR respectively.

Significant improvements in functional class were demonstrated only in subjects on sildenafil high dose compared to placebo. Odds ratios for the sildenafil low, medium and high dose groups compared to placebo were 0.6 (95% CI: 0.18, 2.01), 2.25 (95% CI: 0.75, 6.69) and 4.52 (95% CI: 1.56, 13.10), respectively.

Long-term extension data

Of the 234 pediatric subjects treated in the short-term, placebo-controlled study, 220 subjects entered the long-term extension study. Subjects who had been in the placebo group in the short-term study were randomly reassigned to sildenafil treatment; subjects weighing ≤20 kg entered the medium or high dose groups (1:1), while subjects weighing >20 kg entered the low, medium or high dose groups (1:1:1). Of the total 229 subjects who received sildenafil, there were 55, 74, and 100 subjects in the low, medium and high dose groups, respectively. Across the short-term and long-term studies, the overall duration of treatment from start of double-blind for individual subjects ranged from 3 to 3129 days. By sildenafil treatment group, median duration of sildenafil treatment was 1696 days (excluding the 5 subjects who received placebo in double-blind and were not treated in the long-term extension study).

Peak VO_2 was assessed 1 year after the start of the placebo-controlled study. Of those sildenafil treated subjects developmentally able to perform the CPET 59/114 subjects (52%)

had not shown any deterioration in Peak VO_2 from start of sildenafil. Similarly 191 of 229 subjects (83%) who had received sildenafil had either maintained or improved their WHO Functional Class at 1 year assessment.

Kaplan-Meier estimates of survival at 3 years in patients >20 kg in weight at baseline were 94%, 93% and 85% in the low, medium and high dose groups, respectively; for patients ≤20 kg in weight at baseline, the survival estimates were 94% and 93% for subjects in the medium and high dose groups respectively (see sections 4.4 and 4.8).

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%).

Bioequivalence was established between the 20 mg tablet and the 10 mg/mL oral suspension when administered as a 20 mg single oral dose of sildenafil (as citrate).

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.

Pediatric Patients
From a population PK model, body weight was shown to be a good predictor of drug exposure in children. Sildenafil plasma concentration half-life values were estimated to range from 4.2 to 4.4 hours for a range of 10 to 70 kg of body weight and did not show any differences that would appear as clinically relevant. The typical steady state C_{max} and AUC values following a 10 mg three times a day regimen to a 8 kg patient are expected to be 138 ng/mL and 1551 ng*hr/mL, respectively. The typical steady state C_{max} and AUC values following a 20 mg three times a day regimen to a 20 kg patient are expected to be 168 ng/mL and 1696 ng*hr/mL, respectively. T_{max} was estimated at approximately 1 hour and was almost independent from body weight.

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
Sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide, sodium benzoate, colloidal silicon dioxide anhydrous, grape flavor

6.2. Incompatibilities
This medicinal product should not be mixed with any other medication or additional flavoring agent. The oral suspension should not be further diluted with water or other vehicles.

6.3. Shelf life
2 years

After reconstitution, the oral suspension is stable for 30 days.

6.4. Special precautions for storage

Powder for oral suspension:
Do not store above 30°C.

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

Reconstituted oral suspension:
Store below 30°C or in refrigerator at 2 to 8°C. Do not freeze.

6.5. Nature and contents of container

One 125 mL amber glass bottle (with a polypropylene closure) contains 32.27 g of powder for oral suspension.

Once reconstituted the bottle contains 112 mL of oral suspension, providing a usable volume of 90 mL which is intended for dosing and administration.

6.6. Special precautions for disposal and other handling

Any unused product should be disposed of in accordance with local requirements.

Reconstitution instructions:
Note: A total volume of 90 mL of water irrespective of the dose you are taking should be used to reconstitute the contents of the bottle.

1. Tap the bottle to release the powder.
2. Remove the cap.
3. Accurately measure out 60 mL of water and pour the water into the bottle.
4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds (Figure 2).

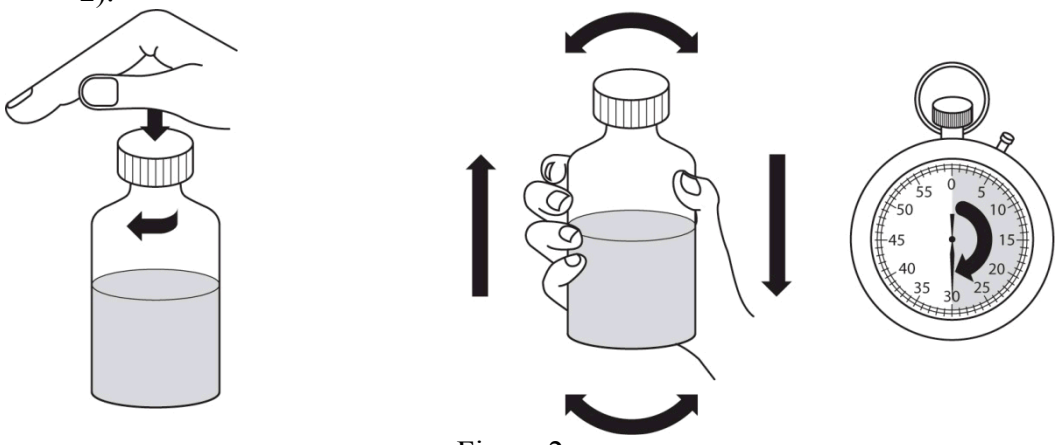

Figure 2

5. Remove the cap.
6. Accurately measure out another 30 mL of water and add this to the bottle. You should

always add a total of 90 mL of water irrespective of the dose prescribed.

7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds (Figure 3).

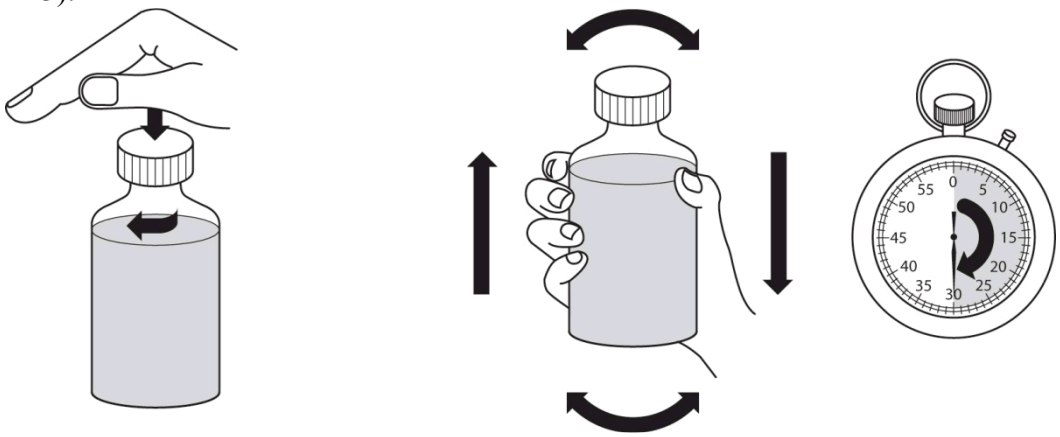

Figure 3

8. Remove the cap.
9. When reconstituted the powder provides a white grape flavored oral suspension. Write the expiration date of the reconstituted oral suspension on the bottle label (the expiration date of the reconstituted oral suspension is 30 days from the date of reconstitution). Any unused oral suspension should be discarded or returned to your pharmacist after this date.

Instructions for use:
Revatio for oral suspension should not be mixed with any other medication or flavoring agent. The oral suspension should not be further diluted with water or other liquid.

1. Shake the closed bottle of reconstituted oral suspension vigorously for a minimum of 10 seconds before use. Remove the cap (Figure 4).

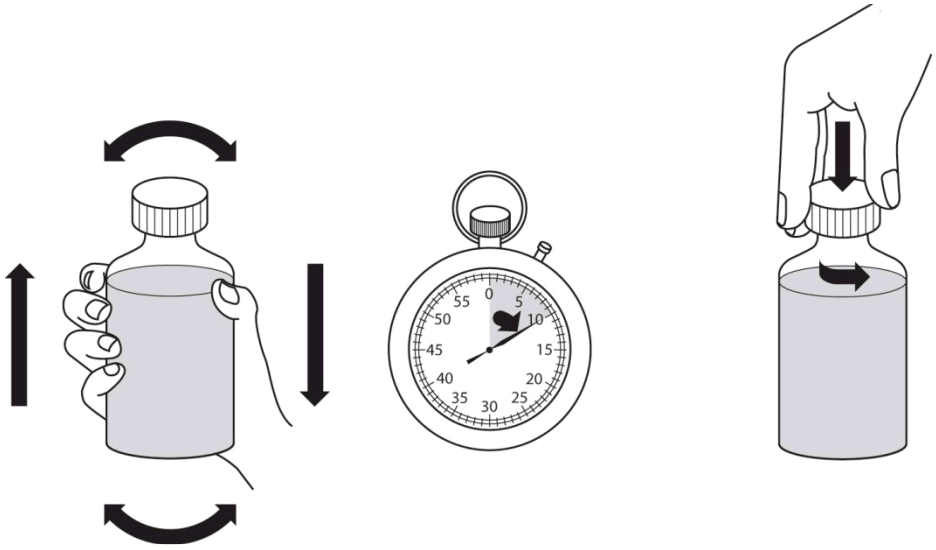

Figure 4

2. Consider dispensing the suspension with an appropriate graduated oral syringe for measuring the required volumes of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (1 ml or 2 ml) on the oral syringe for each patient.

7. MARKETING AUTHORISATION HOLDER
Manufactured by:
Fareva Amboise
Pocé-sur-Cisse, France

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER
Box, 1 bottle @ 112 mL; Reg. No.: DKI1990401538A1

HARUS DENGAN RESEP DOKTER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
NA

10. DATE OF REVISION OF THE TEXT
7/2019
CDS version 11