AUSTRALIAN PRODUCT INFORMATION – REVATIO® (sildenafil citrate)

1. NAME OF THE MEDICINE

Sildenafil citrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REVATIO tablets contain 20 mg sildenafil (as the citrate)

REVATIO solution for injection contains 10 mg sildenafil (as citrate) in 12.5 ml .

Excipient(s) with known effect

- Lactose (REVATIO tablets only)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablets

REVATIO tablets are white to off-white, round biconvex, debossed, film coated tablets.

Solution for injection

REVATIO solution for injection is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REVATIO tablets are indicated for the treatment of patients with pulmonary arterial hypertension classified as WHO functional classes II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

REVATIO solution for injection is for the treatment of adult patients with pulmonary arterial hypertension who are currently prescribed oral REVATIO and who are temporarily unable to take oral therapy, but are otherwise clinically and haemodynamically stable.

The efficacy of REVATIO has not been established in patients currently on bosentan therapy (see Section 4.4 Special precautions and warnings for use).

4.2 Dose and method of administration

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension. In case of clinical deterioration in spite of REVATIO treatment, alternative therapies should be considered.

Use in adults (≥18 years)

Oral Tablet

The recommended dose for REVATIO is 20 mg TID. REVATIO tablets should be taken approximately 6-8 hours apart, with or without food.

No greater efficacy was achieved with doses higher than 20 mg TID, therefore, treatment with doses higher than 20 mg TID is not recommended (see Section 5.1 Pharmacological Properties, Clinical Trials). Dosages lower than 20 mg TID have not been examined and the efficacy of these doses is not known.

Intravenous Solution

REVATIO solution for injection should only be administered to patients unable to take oral therapy and who have tolerated and responded to stable oral therapy. Intravenous sildenafil should not be used to initiate therapy.

Intravenous sildenafil should only be administered by a Health Care Professional who is experienced in the management of pulmonary artery hypertension. Patients should be monitored for hypotension.

The 10 mg intravenous TID dose of sildenafil is expected to match the total PDE5 inhibition achieved with the 20 mg REVATIO TID oral dose, based on population PK modelling.

REVATIO solution for injection is for intravenous use as a bolus injection.

The recommended dose is 10 mg (corresponding to 12.5 mL) three times a day administered as an intravenous bolus injection.

REVATIO solution for injection contains no antimicrobial preservative. Use in one patient on one occasion only. Discard any residue. Each dose requires a new vial.

Incompatibilities:

Chemical and physical compatibility has been demonstrated with the following diluents:

- 5% glucose solution
- 0.9% sodium chloride solution
- Lactated Ringer's solution
- 5% glucose/0.45% sodium chloride solution
- 5% glucose/lactated Ringer's solution
- 5% glucose/20 mEq potassium chloride solution.

Use in children (<18 Years)

REVATIO is not indicated for use in children <18 years of age.

Discontinuation of treatment

Limited data suggests that the abrupt discontinuation of REVATIO is not associated with rebound worsening of pulmonary arterial hypertension. However to avoid the possible occurrence of sudden clinical deterioration during withdrawal, a gradual dose reduction should be considered. Intensified monitoring is recommended during the discontinuation period.

Dosage adjustment

Dosage Adjustment in the Elderly (>65 years of age)

In general, dose selection of sildenafil for elderly PAH patients should be undertaken cautiously due to higher incidence of compromised renal, hepatic or cardiac function, and of concomitant disease or drug therapy (see Section 5.2, Pharmacokinetics, Elderly (>65 years of age)).

Dosage Adjustment in Renal Impairment

Oral therapy: Initial dose adjustments are not required in patients with renal impairment. A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

Intravenous therapy: Initial dose adjustments are not required in patients with renal impairment, including severe renal impairment (creatinine clearance <30 mL/min). A downward dose adjustment to 10 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated (see Section 5.2, Pharmacokinetics, Renal Impairment regarding increased exposure in patients with severe renal impairment).

Dosage Adjustment in Hepatic Impairment

Oral therapy: Initial dose adjustments are not required in patients with hepatic impairment (Child-Pugh class A and B). A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if oral therapy is not well-tolerated.

Intravenous therapy: Initial dose adjustments are not required in patients with hepatic impairment (Child-Pugh class A and B). A downward dose adjustment to 10 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

REVATIO is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) (see Section 5.2, Pharmacokinetics, Hepatic Impairment).

Co-administration with other PAH treatments

The safety and efficacy of sildenafil when co-administered with medicines for PAH other than epoprostenol has not been studied in controlled clinical trials. Caution is recommended in the case of co-administration. The safety and efficacy of REVATIO when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients.

Use with CYP3A4 Inhibitors and CYP3A4 Inducers

Refer to Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions for dosing instructions.

Refer also to Section 5.1 Pharmacology and Section 5.2 Pharmacokinetics section for information regarding the pharmacokinetics of the intravenous formulation.

4.3 Contraindications

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

Nitrates and REVATIO must not be used concomitantly. Sildenafil was shown to potentiate the hypotensive effects of both acute and chronic nitrate administration and therefore, its co-administration with nitric oxide donors, organic nitrates or organic nitrites in any form, either regularly or intermittently is contraindicated. Drugs which must not be used concomitantly include glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form.

Combination with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir).

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

REVATIO is not recommended in patients with pulmonary arterial hypertension with a previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (see Section 4.4 Special precautions and warnings for use, Section 4.8 Adverse effects (undesirable effects), Post Marketing Experience, Other Events).

The safety of sildenafil has not been studied in the following sub groups of patients and its use is, therefore, contraindicated: severe hepatic impairment, severe hypotension (blood pressure <90/50 mmHg) at initiation, recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of patients have genetic disorders of retinal phosphodiesterases).

4.4 Special warnings and precautions for use

The efficacy of REVATIO has not been established in patients with severe pulmonary arterial hypertension (functional class IV). If the clinical situation deteriorates, therapies that are recommended for the severe stage of the disease should be considered.

Intravenous administration

No clinical data is available for sildenafil intravenous administration in patients who are clinically or haemodynamically unstable. Its use is accordingly not recommended in these patients.

Vasodilatory effects

Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure and, as such, potentiates the hypotensive effect of nitrates (see Section 4.3 Contraindications). 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.

Coronary artery disease

There are no controlled clinical data on the safety and efficacy of sildenafil in patients with coronary artery disease causing unstable angina, life-threatening arrhythmia within the last 6 months, patients with hypertension (BP>170/110 mHg), or who are currently on bosentan or prostacyclin therapy.

Cardiovascular events

In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse 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.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

Physicians should advise patients to stop use of all PDE5 inhibitors, including REVATIO, and seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors when used in the treatment of male-erectile dysfunction. An observational study evaluating whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION suggests an increase in the risk of NAION with PDE5 inhibitor use. 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. PDE5 inhibitors, including sildenafil, are not recommended in patients with pulmonary arterial hypertension with a previous episode of NAION (see Section 4.3 Contraindications and Section 4.8 Adverse effects (undesirable effects), Post Marketing Experience, Other Events*)*.

Anatomical deformation of the penis and 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 anaemia, multiple myeloma or leukaemia).

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.

Co-administration with alpha-blockers

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals (see Section 4.5 Interactions with other medicines and other forms of interactions). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.

Co-administration with bosentan

In a study of PAH patients (primary PAH and secondary PAH associated with CTD) on bosentan therapy, no incremental benefit (6-MWD) of sildenafil co-administered with bosentan was demonstrated over bosentan alone. 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. Physicians should assess the clinical response when sildenafil is used in combination with bosentan in primary PAH. Co-administration of sildenafil and bosentan in patients with PAH associated with CTD is not recommended (see Section 4.5 Interactions with other medicines and other forms of interactions).

Concomitant use with other PDE5 inhibitors

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

Bleeding disorders or active peptic ulceration

Sildenafil had no effect on bleeding time, including during co-administration with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). 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.

Epistaxis in patients with PAH secondary to connective tissue disease

The incidence of epistaxis was higher in patients with PAH secondary to connective tissue disease (sildenafil 12.9%, placebo 0%) than in PPH patients (sildenafil 3.0%, placebo 2.4%). Incidence was also higher in sildenafil-treated patients with concomitant oral Vitamin K antagonist (8.8% versus 1.7% not treated with concomitant Vitamin K antagonist).

Pulmonary veno occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno occlusive disease. Since there are no clinical data on administration of sildenafil to patients with pulmonary veno occlusive disease, administration of sildenafil to such patients is not recommended.

Diabetic retinopathy

There are limited safety data in patients with diabetic retinopathy. The safety of sildenafil in patients with untreated diabetic retinopathy has not been studied and therefore, sildenafil should be administered to these patients only after careful benefit-risk assessment.

Sudden decrease or loss of hearing

Sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness 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.

Effects on fertility

There was no impairment of fertility in rats given sildenafil for 36 days to females and 102 days to males at plasma exposure levels more than 25 times the human male AUC at an oral dose of 100 mg.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

Use in the elderly

See section 4.2 Dose and method of administration

Paediatric use

REVATIO is not indicated for use in children under 18 years of age.

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interaction

Effect of other medicines on REVATIO

In vitro studies

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies

Population pharmacokinetic analysis of pulmonary arterial hypertension clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. Reduction in sildenafil clearance was also observed when sildenafil was co-administered with mild/moderate CYP3A4 inhibitors and with beta-blockers. These were the only factors with a statistically significant impact on oral sildenafil pharmacokinetics in patients with pulmonary arterial hypertension. The exposure to oral sildenafil in patients on CYP3A4 substrates and CYP3A4 substrates plus beta-blockers was 43% and 66% higher, respectively, compared to patients not receiving these classes of medicines. Sildenafil exposure, without concomitant medication, was 5-fold higher at a dose of 80 mg three times a day compared to the exposure at a dose of 20 mg three times a day. This concentration range covers the increase in oral sildenafil exposure observed in specifically designed drug interaction studies with CYP3A4 inhibitors (except more potent CYP3A4 inhibitors e.g., ketoconazole, itraconazole, ritonavir).

CYP3A4 inducers seemed to have a substantial impact on the pharmacokinetics of oral sildenafil in pulmonary arterial hypertension patients, which was confirmed in the in-vivo interaction study with CYP3A4 inducer bosentan. Concomitant administration of potent CYP3A4 inducers is expected to cause substantial decreases in plasma levels of sildenafil (see Section 4.4 Special precautions and warnings for use).

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 oral sildenafil at steady state (80 mg three times a day) resulted in a 62.6% decrease of sildenafil AUC and a 55.4% decrease in sildenafil C_{max}. The same effect was also observed with lower doses of sildenafil (20 mg three times a day) and bosentan therapy (62.5 mg – 125 mg twice daily). The combination of both drugs did not lead to clinically significant changes of blood pressure (supine and standing).

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

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with oral sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see Section 4.3 Contraindications).

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with oral 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.

When a single 100 mg dose of oral sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182% increase

in sildenafil systemic exposure (AUC). 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 non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with oral sildenafil (50 mg) to healthy volunteers.

Potent CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have effects similar to ritonavir (see Section 4.3 Contraindications). CYP3A4 inhibitors of intermediate potency (e.g., clarithromycin, telithromycin and nefazodone) are expected to have an effect in between that of ritonavir and CYP3A4 inhibitors of medium potency (e.g., saquinavir/erythromycin), a seven-fold increase in exposure is assumed. Therefore, downward dose adjustments are recommended when using CYP3A4 inhibitors of intermediate potency and consideration should be given to a downward dose adjustment when using CYP3A4 inhibitors of medium potency.

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 oral sildenafil exposure compared with administration of CYP3A4 substrates alone.

The mean reduction of sildenafil (80 mg TID) bioavailability due to co-administration of epoprostenol was 28%, resulting in about 22% lower mean average steady state concentrations. Therefore, the slight decrease of sildenafil exposure in the presence of epoprostenol is not considered clinically relevant. The effect of sildenafil on epoprostenol pharmacokinetics is not known.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of oral sildenafil.

Riociguat: Preclinical studies showed an 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 sildenafil. 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 as it may potentially lead to symptomatic hypotension (see Section 4.3 Contraindications).

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

Co-administration of oral contraceptives (ethinyloestradiol 30 μg and levonorgestrel 150 μg) did not affect the pharmacokinetics of oral sildenafil.

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.

Effect of REVATIO on other medicines

In vitro studies

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} >150 microM).

There are no data on the interaction of sildenafil with non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies

In three specific drug - drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and oral sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilised on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilised on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and 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 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

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

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

Oral sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Oral sildenafil causes a small reduction in supine and tilted diastolic blood pressure (3.5 and 6.1 mmHg respectively) in healthy subjects who had a blood alcohol level of 80 mg/dL.

In a study of healthy volunteers oral sildenafil at steady state (80 mg three times a day) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg twice daily). The same effect was also observed with lower doses of sildenafil (20 mg three times a day) and bosentan therapy (62.5 mg – 125 mg twice a day).

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

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

Consistent with its known effects on the nitric oxide/cGMP pathway, 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).

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

Co-administration with other PAH treatments

The safety and efficacy of sildenafil when co-administered with medicines for PAH other than epoprostenol has not been studied in controlled clinical trials. Caution is recommended in the case of co-administration. The safety and efficacy of REVATIO when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 4.4 Special warnings and precautions for use

Use in pregnancy – Pregnancy Category B1.

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits, which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 30 and 70 times the recommended human dose (RHD) on a mg/m^2 basis in a 50 kg subject. In the rat, pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day given for 36 days. In the non-pregnant rat the AUC for unbound sildenafil and its major metabolite at this dose was about 20 times the unbound human AUC at the MHRD of 20 mg three times a day. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Use in lactation

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. There is a lack of information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Prescribers should carefully assess the mother's clinical need for REVATIO and any potential adverse effects on the breastfed child.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed. However, as transient visual disturbances and dizziness have been reported in some patients taking sildenafil, patients should be aware of how they react to sildenafil before driving or operating machinery, and the doctor should advise accordingly.

4.8 Adverse effects (undesirable effects)

Clinical trial in pulmonary arterial hypertension

Safety data were obtained from the pivotal study and an open-label extension study in 277 (207 on REVATIO and 70 on placebo) treated patients with pulmonary arterial hypertension. Following completion of the pivotal study, 259 subjects entered a long-term extension study. Doses up to 80 mg TID (4 times the recommended dose of 20 mg TID) were studied (N=149 patients treated for at least 1 year).

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was low (2.9%) and the same as placebo (2.9%). In the pivotal placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that occurred in at least 3% of REVATIO-treated patients at any of the 20, 40 or 80 mg TID doses, and more commonly on REVATIO than on placebo are shown in Table 1.

Table 1: Sildenafil Adverse Events More Frequent than Placebo in ≥3% of Patients.

ADVERSE EVENT (%)	Placebo (N=70)	SILDENAFIL TREATMENT GROUPS			
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)	Total (N=207)
Headache	39	46	42	49	46
Flushing	4	10	9	16	12
Dyspepsia	7	13	8	13	11
Back pain	11	13	13	9	12
Diarrhoea	6	9	12	10	10
Limb pain	6	7	15	9	10
Myalgia	4	7	6	14	9
Cough	6	7	5	9	7
Epistaxis	1	9	8	4	7
Pyrexia	3	6	3	10	6
Influenza	3	6	6	4	5
Vertigo	1	1	5	3	3
Gastritis	0	3	3	4	3
Erythema	0	6	2	1	3
Insomnia	1	7	6	4	6
Visual disturbance*	0	0	5	7	4
Dyspnoea (exacerbated)	3	7	2	1	3
Sinusitis	0	3	5	1	3
Paresthesia	0	3	5	1	3
Rhinitis	0	4	2	3	3

*Visual disturbance: Mild and transient, predominately colour tinge to vision, but also increased sensitivity to light, or blurred vision.

The adverse reactions that occurred in ≥1% and <3% and more frequently with REVATIO than with placebo were the following:

Blood and lymphatic disorders: Anaemia NOS.

Ear: Vertigo.

Eye disorders: Abnormal sensation in eye, chromatopsia, cyanopsia, diplopia, eye irritation, photophobia, retinal haemorrhage, visual acuity reduced.

Gastrointestinal disorders: Abdominal distension, gastritis (not otherwise specified, NOS), gastroenteritis NOS, gastroesophageal reflux disease, haemorrhoids.

Infections and infestations: Sinusitis NOS, cellulitus.

Investigations: Weight increased.

Metabolism disorders: Fluid retention.

Nervous system disorders: Paraesthesia, tremor, burning sensation NOS, migraine NOS, hypoaesthesia.

Psychiatric disorders: Anxiety.

Respiratory, thoracic and mediastinal disorders: Bronchitis NOS, rhinitis NOS.

Reproductive system disorders: Gynaecomastia.

Skin and subcutaneous tissue disorders: Alopecia, erythema.

Intravenous Administration

Study A1481262 was a single centre, single dose, open label study to assess the safety and efficacy, tolerability and pharmacokinetics of a single intravenous dose of sildenafil (10 mg) administered as a bolus injection to patients with PAH who were already receiving and stable on oral REVATIO 20 mg TID.

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 events (flushing, flatulence and hot flush). There was one serious adverse event in a subject with severe ischaemic cardiomyopathy who experienced ventricular fibrillation and death 6 days post study drug; it was judged to be unrelated to study drug.

Post marketing experience

Cardiovascular

In post marketing experience at doses indicated for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack and hypertension, have been reported post marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's

underlying cardiovascular disease, to a combination of these factors, or to other factors. Tachycardia, hypotension, syncope, and epistaxis have also been reported post marketing.

Other Events

When used to treat male-erectile dysfunction, non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil citrate. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking. An observational study evaluating whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION suggests an increase in the risk of NAION with PDE5 inhibitor use (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

Cases of sudden decrease or loss of hearing have been reported post-marketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors (see Section 4.4. Special warnings and precautions for use).

Other events, reported post marketing at the indicated dose or doses indicated for male erectile dysfunction, to have been observed in temporal association with sildenafil and not listed in the clinical trials adverse reactions section include:

Immune system disorders: Hypersensitivity (including skin rash).

Gastrointestinal disorders: Vomiting, nausea.

Eye disorders: Eye pain, red eyes/bloodshot eyes.

Reproductive system and breast disorders: Prolonged erection and/or priapism.

Musculoskeletal and connective tissue disorders: Pain in extremity/pain in jaw/arthralgia.

Respiratory, thoracic and mediastinal disorders: Nasal congestion.

Vascular disorders: Hypotension.

Cardiac disorders: Cardiac arrest.

General disorders and administration site conditions: Oedema/peripheral oedema.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdose information is limited. In studies with healthy volunteers, of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Sildenafil blood levels are not clinically useful. Monitor ECG and blood pressure in symptomatic patients. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

REVATIO, a therapy for pulmonary arterial hypertension, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5). Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to selective vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. 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.

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity observed *in vitro*, and the mild peripheral arterial-venous dilatation *in vivo*.

Clinical trials

Sildenafil causes mild and transient decreases in systemic blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decrease in supine systolic blood pressure following 100 mg oral dosing of sildenafil was 8.3 mmHg. The corresponding change in supine diastolic blood pressure was 5.3 mmHg. After chronic dosing of 80 mg three times a day to healthy male volunteers, the largest average change from baseline of supine systolic blood pressure was a decrease of 9.0 mmHg. The corresponding change in supine diastolic blood pressure was a decrease of 8.4 mmHg.

After chronic dosing of 80 mg three times a day to patients with systemic hypertension the mean change from baseline in systolic and diastolic blood pressure was a decrease of 9.4 mmHg and 9.1 mm Hg respectively.

After chronic dosing of 80 mg three times a day to patients with pulmonary arterial hypertension lesser effects in blood pressure reduction were observed (a reduction in both systolic and diastolic pressure of 2 mmHg). This may be due to improvements in cardiac output secondary to the beneficial effects of sildenafil on pulmonary vascular resistance.

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg three times a day to patients with pulmonary arterial hypertension no clinically relevant effects on the ECG were reported.

Sildenafil has no effect on visual acuity or contrast sensitivity. Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose.

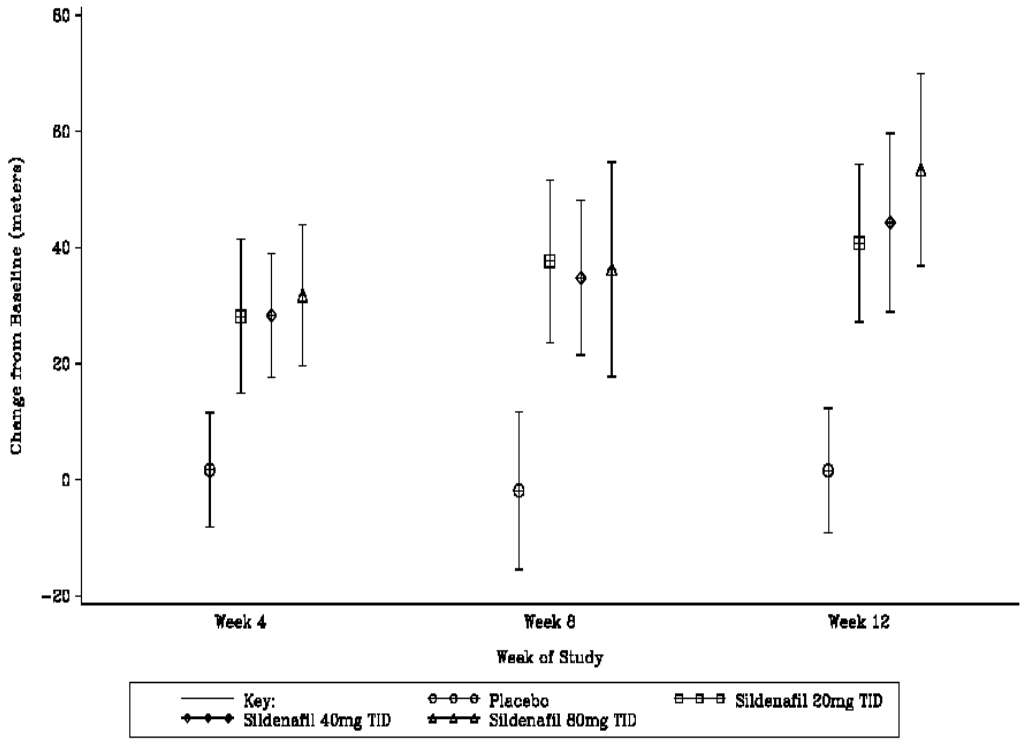
The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. *In vitro* studies show that sildenafil is 10-fold less potent against PDE6 than PDE5.

A randomised, double-blind, placebo-controlled study (A1481140) was conducted in 277 patients with pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure of ≥25 mmHg at rest with a pulmonary capillary wedge pressure <15 mmHg. Allowed background therapy included a combination of anticoagulation, digoxin, calcium channel blockers, diuretics or oxygen. The use of prostacyclin analogues, endothelin receptor antagonists, and arginine supplementation were not permitted. Subjects who had failed to respond to bosentan were also excluded. Patients with left ventricular ejection fraction <45% or left ventricular shortening fraction <0.2 also were not studied.

Patients were randomised to receive placebo (n=70) or REVATIO 20 mg (n=69), 40 mg (n=67) or 80 mg (n=71) (TID) for a period of 12 weeks. They had either primary pulmonary hypertension (63%), PAH associated with connective tissue disease (30%), or PAH following surgical repair of left-to-right congenital heart lesions (7%). The study population consisted of 25% men and 75% women with a mean age of 49 years (range: 18-81 years) and baseline 6-minute walk test distance between 100 and 450 metres. Most patients were functional Class II (107/277, 39%) or Class III (160/277, 58%) with a mean baseline 6 minute walking distance (6-MWD) of 378 meters and 326 meters respectively; fewer patients were Class I (1/277, 0.4%) or IV (9/277, 3%).

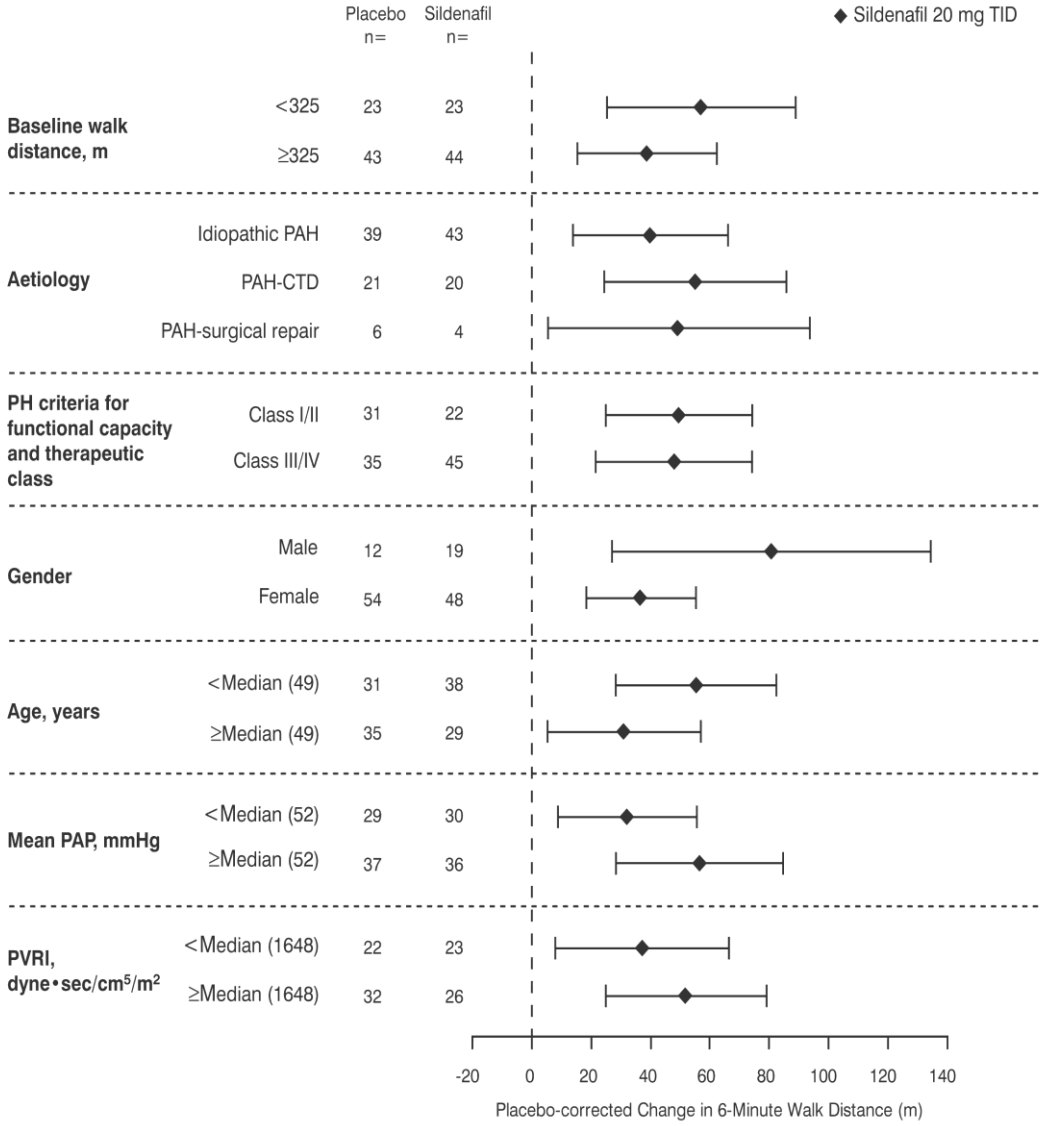
The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance. A statistically significant increase in 6-minute walk distance was observed in all 3 sildenafil dose groups compared to those on placebo. Placebo corrected increases in walk distance were 45 metres ($p < 0.0001$), 46 metres ($p < 0.0001$) and 50 metres ($p < 0.0001$) for sildenafil 20 mg, 40 mg and 80 mg respectively. There was no significant difference in effect between sildenafil doses (see Figure 1).

Figure 1: Change from Baseline in 6-Minute Walk Distance (metres): Mean (95% Confidence Interval)



The improvement in walk distance was apparent after 4 weeks of treatment and this effect was maintained at weeks 8 and 12. Results were generally consistent in subgroups according to baseline walking distance, aetiology (primary and Connective Tissue Disease (CTD)-associated PAH), WHO functional class, gender, race, location, mean Pulmonary Arterial Pressure (PAP) and Pulmonary Vascular Resistance Index (PVARI) (see Figure 2).

Figure 2: Placebo Corrected Change From Baseline in 6-Minute Walk Distance (metres) by study subpopulation: Mean (95% Confidence Interval)



Key: PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PH, pulmonary hypertension; PAP = pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; TID = three times daily.

Patients on all REVATIO doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo. Doses of 20 mg, 40 mg, and 80 mg TID produced a placebo-corrected decrease in mPAP of -2.7 mmHg, -3.0 mmHg, and -5.1 mmHg, respectively. These comparisons to placebo were planned, but no pre-defined comparisons were specified between sildenafil dose groups. Summaries of changes from baseline for haemodynamic parameters can be found in Table 2.

Table 2: Changes from Baseline to Week 12 in Haemodynamic Parameters at Sildenafil 20 mg TID Dose, 40 mg TID Dose and 80 mg TID Dose

PARAMETER [mean (95% CI)]	Placebo (N=65)*	Sildenafil 20 mg TID (N=65)*	Sildenafil 40 mg TID (N=65)*	Sildenafil 80 mg TID (N=65)*
mPAP	0.6 (-0.8, 2.0)	-2.1 (-4.3, 0.0)	-2.6 (-4.4, -0.9)	-4.7 (-6.7, -2.8)
PVR (dyn·s/cm^5)	49 (-54, 153)	-122 (-217, -27)	-143 (-218, -69)	-261 (-365, -157)
SVR (dyn·s/cm^5)	-78 (-197, 41)	-167 (-307, -26)	-258 (-401, -114)	-323 (-451, -195)
RAP (mmHg)	0.3 (-0.9, 1.5)	-0.8 (-1.9, 0.3)	-1.1 (-2.4, 0.2)	-1.0 (-2.1, 0.1)
CO (L/min)	-0.1 (-0.4, 0.2)	0.4 (0.1, 0.7)	0.4 (0.1, 0.8)	0.7 (0.4, 1.0)
HR (beats/min)	-1.3 (-4.1, 1.4)	-3.7 (-5.9, -1.4)	-3.3 (-5.5, -1.0)	-4.7, (-7.3, -2.2)

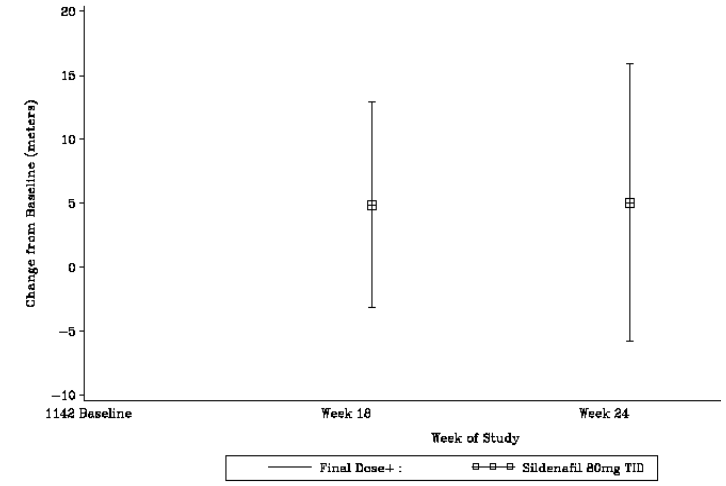
∗The number of patients per treatment group varied slightly for each parameter due to missing assessments.PAH – mean pulmonary arterial pressure; PVR – pulmonary vascular resistance; SVR – systemic vascular resistance; RAP – right atrial pressure; CO – cardiac output; HR – heart rate

Extension Study

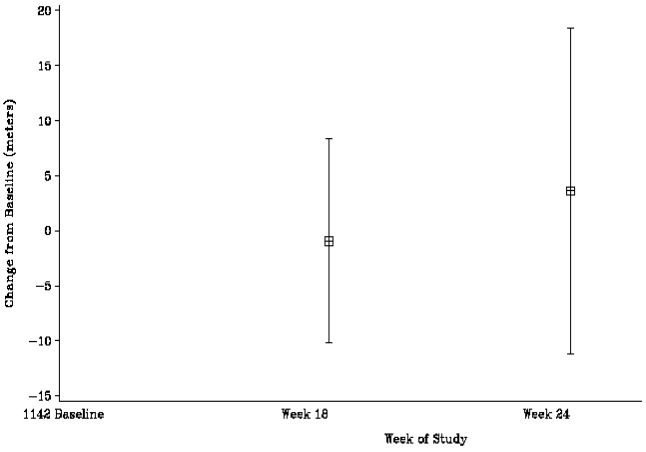
Following the pivotal study, 259 of the 277 REVATIO-treated patients entered an extension study, for which an interim data analysis was performed after 24 weeks of therapy. In the extension study, patients were allocated to either one of two dosage regimens (A or B). In regimen A patients received 40 mg sildenafil TID for 6 weeks and were then titrated to 80 mg TID for the remainder of the study. In regimen B, patients received 80 mg sildenafil TID for 6 weeks and were then dummy titrated to 80 mg TID. Patients who had initially been on 20 mg TID or 40 mg TID were allocated to regimen A while those initially on 80 mg TID were allocated to continue 80 mg TID in Regimen B. Patients could be down-titrated if they did not tolerate the 40 mg TID or 80 mg TID dose. There was no placebo arm in the extension study. Results of the extension study are represented in Figure 3.

Figure 3: Changes in 6-Minute Walk distance from A1481142 baseline to Week 24 for patients randomised in Study A1481140 to sildenafil 20 mg TID (A), sildenafil 40 mg TID (B), and sildenafil 80 mg TID (C)

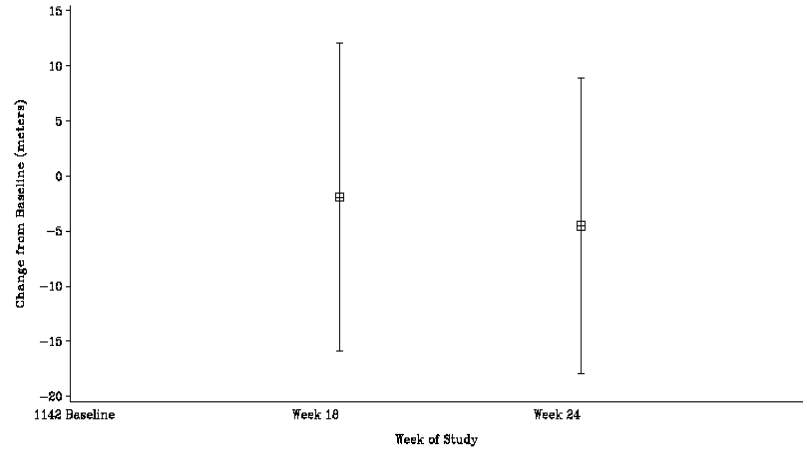
(A)



(B)



(C)



The long term effects of REVATIO on mortality or functional class have not been established.

Efficacy in adult patients with PAH when used in combination with epoprostenol

A randomised, double-blind, placebo controlled study (A1481141) was conducted in 265 patients with PAH who were stabilised on intravenous epoprostenol (131 to placebo and 134 to sildenafil). The PAH patients included those with Primary PAH, PAH associated with CTD and PAH following surgical repair of congenital heart lesions. Patients were randomised to placebo or subject-optimized dose of sildenafil (20, 40, or 80 mg sildenafil TID). Patients started with 20 mg for the first 4 weeks and were then titrated to 40 mg for 4 weeks, and then to 80 mg for 8 weeks. Subjects were allowed to down titrate after each increase if unable to tolerate the higher dose.

The primary efficacy endpoint was the change from baseline at week 16 in 6-minute walk distance. For the ITT population there was a statistically significant benefit of sildenafil compared to placebo in 6-minute walk distance. The mean change from baseline at week 16 was 30.1m for the sildenafil group compared with 4.1m for the placebo group, giving an adjusted treatment difference of 26.0 m (95% CI: 10.8, 41.2) (p=0.0009) (ANOVA). 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 favour of sildenafil (95% CI: -5.7, -2.1) (p=0.00003) (ANOVA). A summary of Change from Baseline to Week 16 (LOCF) in Pulmonary Hypertension Criteria for Functional Capacity and Therapeutic Class (ITT Population) is presented in Table 3.

Table 3: Summary of Change from Baseline to Week 16 (LOCF) in Pulmonary Hypertension Criteria for Functional Capacity and Therapeutic Class (ITT Population)

Treatment group	**Functional class at week 16 (LOCF)**	**Functional class at baseline**			
		I n (%)	II n (%)	III n (%)	IV n (%)
	I	2 (1.6)	1 (0.8)	0	0
Placebo	II	0	25 (20.0)	16 (12.8)	0
(n = 125)	III	0	8 (6.4)	62 (49.6)	1 (0.8)
	IV	0	0	7 (5.6)	3 (2.4)
	I	1 (0.8)	8 (6.1)	1 (0.8)	0
Sildenafil	II	0	21 (15.9)	31 (23.5)	0
(n = 132)	III	0	5 (3.8)	51 (38.6)	7 (5.3)
	IV	0	0	4 (3.0)	3 (2.3)

LOCF = last observation carried forward

Delay to 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).

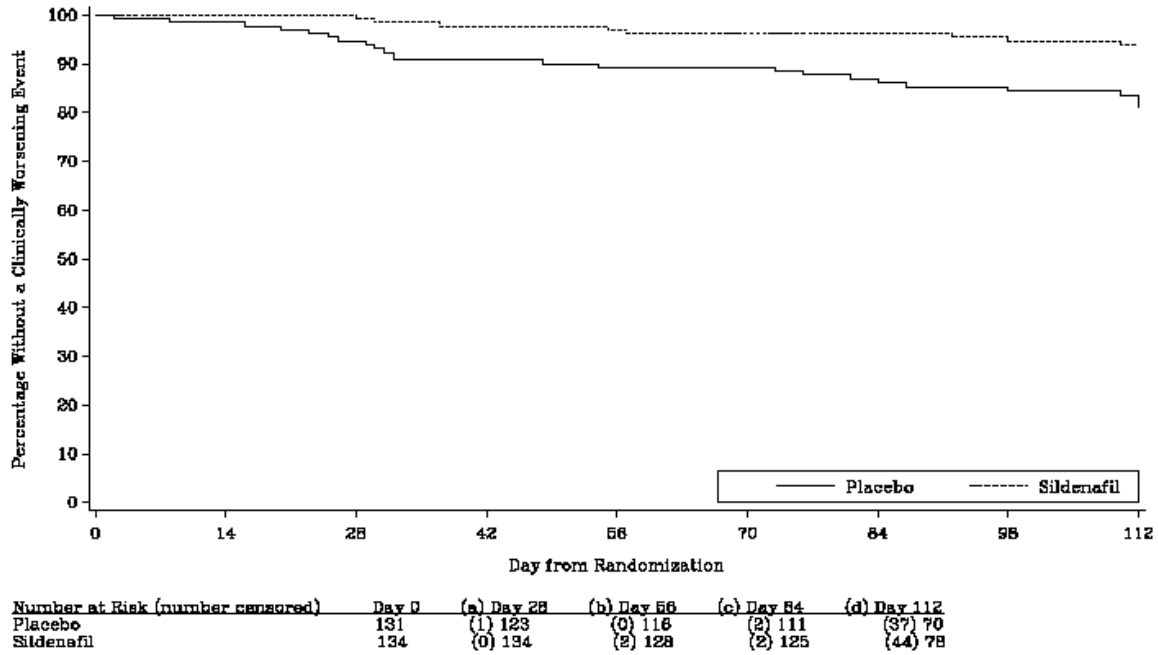
Time to clinical worsening was defined as the time from randomisation to the first occurrence of a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, hospitalisation due to PAH, or clinical deterioration requiring a change in epoprostenol therapy).

Table 4: Summary of Clinical Worsening (ITT Population)

Reason for Clinical Worsening	Placebo (N=131)	Sildenafil (N=134)
Overall number of subjects with clinical worsening, n (%)	23 (17.6)	8 (6.0)
Clinical worsening event		
Deaths during A1481141*	4 (3.1)	0
Hospitalisation due to PAH	11 (8.4)	8 (6.0)
Lung transplantation	1 (0.8)	0
Change in epoprostenol dose	16 (12.2)	2 (1.5)
Initiation of bosentan	1 (0.8)	0
Life table estimates of clinical worsening by day 112		
Proportion worsened	0.187	0.062
95% CI	0.117, 0.257	0.020, 0.104

* 4 deaths occurred during the study; an additional 4 deaths occurred after the end of the study (1 sildenafil, 3 placebo)

Figure 4: Kaplan-Meier Plot of Time to Clinical Worsening (Days) (ITT Population)



The numbers censored are given in parentheses and represent the number of subjects censored between a) Days 0 and 27, b) Days 28 and 55, c) Days 56 and 83 and d) Days 84 and 111. There are 30 and 38 subjects censored between Days 108 and 111 in the placebo and sildenafil groups, respectively. This is due to subjects completing their Week 16 visit according to the protocol-specified windows (Day 112 ± 3 days).

The Kaplan-Meier curves in Figure 4 show separation between treatment groups occurred as early as the Week 4 visit, when all of sildenafil/epoprostenol subjects were on the 20 mg TID dose.

Efficacy and pharmacokinetics of intravenous sildenafil in adult patients with PAH

Study A1481262 was a single centre, single dose, 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 already receiving and stable on oral REVATIO 20 mg. A total of 10 PAH subjects enrolled and completed the study. Eight subjects were taking bosentan and one subject was taking treprostinil in addition to bosentan and REVATIO. After dosing, sitting and standing blood pressure and heart rate were recorded at 30, 60, 120, 180 and 360 minutes post dose. The mean changes from baseline in sitting blood pressure were greatest at 1 hour, -9.1 mmHg (SD ± 12.5) and -3.0 (SD ± 4.9) mmHg for systolic and diastolic pressure respectively. The mean postural changes in systolic and diastolic blood pressure over time were small (<10 mmHg) and returned towards baseline beyond 2 hours.

The 10 mg intravenous TID dose of sildenafil is expected to match the total PDE5 inhibition achieved with the 20 mg REVATIO TID oral dose. No data were generated to demonstrate that the intravenous and oral formulations of sildenafil have comparable efficacy. It should be noted that the data supporting the intravenous dosing is based on pharmacokinetic data only.

Paediatric Clinical Trial Safety Data

In a placebo-controlled study of REVATIO in patients 1 to 17 years of age with pulmonary arterial hypertension, a total of 174 patients were treated three times a day with either low (10 mg in patients > 20 kg; no patients ≤ 20 kg received the low dose), medium (10 mg in patients 8-20 kg; 20 mg in patients 20-45 kg; 40 mg in patients > 45 kg) or high dose (20 mg in patients 8-20 kg; 40 mg in patients 20-45 kg; 80 mg in patients > 45 kg) regimens of REVATIO and 60 were treated with placebo.

In the placebo-controlled study of 16 weeks, the adverse reactions profile seen in this paediatric study was generally consistent with that in adults. The most common treatment-related AEs (TRAEs) that occurred (with a frequency ≥ 1% in a sildenafil group) and with a frequency > 1% between combined doses of sildenafil and placebo, in the paediatric study were vomiting (5.2%), cough, pyrexia, (each 1.7%) and nausea, abdominal pain lower, abdominal pain upper, photophobia (each 1.1%). TRAEs erection increased and spontaneous penile erections occurred with a combined frequency of 9.0% in male subjects in the combined sildenafil group. Most of these TRAEs were mild or moderate in severity. Other commonly reported adverse reactions include upper respiratory tract infection (URTI), bronchitis, pharyngitis, pneumonia and rhinorrhoea.

Following completion of the 16 week placebo-controlled study, 220 subjects entered a long-term extension study. Subjects who had been on active therapy continued in the same treatment regimen, whilst those who had been on placebo therapy for 16 weeks were randomised to low, medium or high dose groups of sildenafil.

At two years, 184 subjects were still participating in the extension study. Over the first two years of sildenafil dosing a total of 4 of the 229 subjects who received sildenafil had a serious adverse reaction; 1 of 74 subjects in the medium dose group and 3 of 100 subjects in the high dose group. These 4 events were convulsion, hypersensitivity, hypoxia and ventricular arrhythmia.

From a data cut with a median subject duration of treatment of 2.2 years (range: 0 to 5.0 years) the most frequently reported treatment related AEs were: headache (13.2%), erection increased (9.0%), vomiting (6.8%), abdominal pain (3.4%) cough and dyspepsia (each 2.6%).

Kaplan-Meier estimates of survival at 3 years, in patients > 20 kg in weight at baseline, were 92%, 90% and 84% in the low, medium and high dose groups respectively; for patients ≤ 20 kg in weight at baseline, the survival estimates were 93% and 94% for subjects in the medium and high dose groups respectively.

From a data-cut > 7 years after the study start (median follow up of 4 years (range of 0.3 to 7.0 years) and median duration of sildenafil treatment of about 4 years (range of 3 days to 7.0 years), 35 deaths were reported, whether on treatment or reported as part of the survival follow-up. The incidence of deaths in the high, medium and low dose groups was 20% (20 of 100), 14% (10 of 74) and 9% (5 of 55) respectively. Causes of death were typical of patients with PAH.

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 doses of 80 mg three times a day, a more than dose proportional increase in sildenafil plasma levels has been observed. In pulmonary arterial hypertension patients, the oral bioavailability of sildenafil after 80 mg three times a day was on average 43% (90% CI: 27% - 60%) higher compared to the lower doses.

When oral sildenafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

The pharmacokinetic profile of REVATIO solution for injection has been characterised following intravenous administration. A 10 mg dose of REVATIO IV Solution for Injection is predicted to provide a pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose. The geometric means of observed sildenafil C_{max} and AUC (from zero to 8 hours) were 213.3 ng/mL and 329.7 ng.h/mL, respectively, following a 10 mg single intravenous bolus dose.

Distribution

The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. After oral doses of 20 mg three times a day, the mean maximum total plasma concentration of sildenafil at steady state is approximately 113 ng/mL. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% 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 metabolised, with a terminal half-life of approximately 4 hours. In patients with pulmonary arterial hypertension, however, the ratio of the N-desmethyl metabolite to sildenafil is higher. Plasma concentrations of the 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. In healthy volunteers, the plasma levels of the N-desmethyl metabolite following intravenous dosing are significantly lower than those observed following oral dosing. At steady state plasma concentrations of N-desmethyl metabolite are approximately 16% versus 61% those of sildenafil after intravenous and oral dosing respectively.

Excretion

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) to a lesser extent in the urine (approximately 13% of administered oral dose).

Special populations

Elderly (>65 years)

Healthy elderly volunteers (>65 years of age) 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%.

Population pharmacokinetics

Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in pulmonary arterial hypertension patients. None of these factors had a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary hypertension. The data set available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function.

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on the pharmacokinetics in patients with pulmonary arterial hypertension (PAH). The exposure to sildenafil in patients on CYP 3A4 substrates and CYP3A4 substrates plus beta-blockers was 43% and 66% higher respectively, compared to patients not receiving these drug classes.

In patients with pulmonary hypertension, the average steady-state concentrations were 20-50% higher over the investigated dose range of 20-80 mg three times daily (TID), when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary hypertension compared to healthy volunteers.

Renal Impairment

In volunteers with mild (Cl_{cr} = 50-80 mL/min) and moderate (Cl_{cr} = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe ($Cl_{cr} \leq$ 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and C_{max} (88%) compared to age-matched volunteers with no renal impairment.

Hepatic Impairment

In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (85%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severe hepatic impairment has not been studied.

5.3 Preclinical safety data

Genotoxicity

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

Carcinogenicity

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUC) for unbound sildenafil and its major metabolite of 33- and 48-times, for male and female rats, respectively, the exposures observed in human males given the RHD of 20 mg three times a day. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the maximum tolerated dose of 10 mg/kg/day, but resulting in total systemic drug exposure for unbound sildenafil and its major metabolite of less than the exposures observed in human males given the RHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In addition to sildenafil citrate, each REVATIO tablet contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate and triacetin.

In addition to sildenafil citrate, REVATIO 10 mg/12.5 mL solution for injection contains glucose monohydrate .

6.2 Incompatibilities

Section 4.2, Dose and method of administration

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Tablets: Stored below 30°C.

Solution for injection: Stored below 30°C.

6.5 Nature and contents of container

REVATIO 20 mg tablets are presented in PVC/aluminium blister packs containing 90 tablets.

REVATIO 10 mg/12.5 mL solution for injection is supplied in a clear type I glass vial with a chlorobutyl rubber stopper and an aluminium overseal (1 vial/carton).

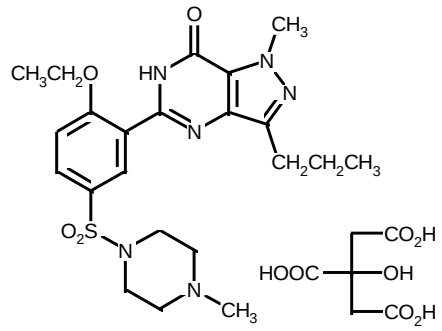
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

Sildenafil citrate is an off-white, crystalline powder with a molecular weight of 666.7. Sildenafil citrate is 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d] pyrimidin-5-yl) phenylsulphonyl]-4-methylpiperazine citrate. The aqueous solubility of sildenafil citrate is equivalent to 2.6 mg sildenafil per mL at 25°C. It has the following structural formula:



The empirical formula for sildenafil citrate is $C_{22}H_{30}N_6O_4S.C_6H_8O_7$.

CAS number

171-599-83-0

7. MEDICINES SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Viatris Pty Ltd
Level 1, 30 The Bond
30-34 Hickson Road
Millers Point NSW 2000
www.viatris.com.au
Phone: 1800 274 276

9. DATE OF FIRST APPROVAL

14 August 2006

10.DATE OF REVISION

14 December 2021

REVATIO® is a Viatris company trade mark

Summary Table of Changes

Section changed	Summary of new information
2	Clarifications for excipient with known effects
All	Editorial changes for cross-reference alignment and section head formatting alignment
8	Sponsor change to “Viatris”