



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Sildenafil

Proprietary Product Name: Revatio

Sponsor: Pfizer Australia Pty Ltd

October 2011

TGA Health Safety
Regulation

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	16 September 2011
<i>Active ingredient(s):</i>	Sildenafil
<i>Product Name(s):</i>	Revatio
<i>Sponsor's Name and Address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
<i>Dose form(s):</i>	Injection solution
<i>Strength(s):</i>	0.8 mg/mL
<i>Container(s):</i>	20 mL and 50 mL type I glass vials
<i>Pack size(s):</i>	1 vial
<i>Approved Therapeutic use:</i>	<p>Oral Revatio is 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.</p> <p>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.</p> <p>The efficacy of Revatio has not been evaluated in patients currently on bosentan therapy.</p>
<i>Route(s) of administration:</i>	Intravenous injection
<i>Dosage:</i>	Bolus injection of 10 mg three times daily
<i>ARTG Numbers:</i>	119102 (tablets), 171474 (solution for injection 10 mg/12.5 mL), 181249 (solution for injection, 40 mg/50 mL).

Product Background

Sildenafil citrate was originally approved in 1998 as an oral formulation for the treatment of erectile dysfunction. It is a potent and specific inhibitor of phosphodiesterase type 5 which enhances vasodilation by inhibiting the catabolism of cyclic guanosine monophosphate (GMP). It was subsequently approved for the treatment of pulmonary arterial hypertension under the trade name Revatio at a dose of 20 mg three times daily in 2005.

This AusPAR describes the evaluation of an application by Pfizer Australia Pty Ltd (the sponsor) for registration of a new solution for injection dosage form of Revatio for intravenous administration with a new indication specific to this presentation along with a slight revision to the current indication. The proposed dosage is 10 mg (one vial containing 12.5 mL of sildenafil citrate 0.8 mg per mL) three times daily.

The proposed indication is:

Revatio solution for injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III who are currently prescribed oral Revatio and who are temporarily unable to take oral medication.

The existing indication is:

Oral Revatio is used 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 is approved for the treatment of patients aged greater than or equal to 18 years. No changes to the indicated population are proposed in this application but there was a concurrent application for paediatric treatment.¹

Regulatory Status

The product received initial ARTG Registration in 2005.

Sildenafil citrate has been approved as an oral therapy for PAH to improve exercise capacity in adult patients since 3 June 2005 in the United States (US), 28 October 2005 in the European Union (EU), 20 July 2007 in New Zealand and 26 May 2006 in Canada. The sponsor identified that identical submissions to this Australian application, except that they contained data relevant to the 50 mg vial only, had been approved in the USA on 18 November 2009, EU on 10 December 2009 and Canada on 14 January 2010. An application to replace the 50 mL vial with a 20 mL vial was approved in the EU on 21 January 2011.

In Europe, it was approved with a specific indication similar to that applied for in this submission but specifying adults only and not applying to the paediatric indication.

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.

In the USA it was not given an indication but added as an approved presentation with instructions in the Dosage section of the US PI.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Chemistry and Quality Control

The control of the sildenafil citrate used in these products is almost the same as the control of that used in the tablets except the limit for an impurity has been tightened and the material was tested for endotoxins with a specified limit. Particle size distribution is controlled even though this is not an issue as the material is fully dissolved in the finished product.

¹ TGA. AusPAR for sildenafil. Available at: <http://www.tga.gov.au/pdf/auspar/auspar-revatio paed.pdf>

Drug Product

The injection solutions are to be manufactured by a single site: Pfizer PGM in France. The process is typical and involves dissolution of ingredients, filtration, filling and terminal sterilisation. The sterility aspects of the manufacture were controlled to the satisfaction of the Microbiology Section of the Office of Laboratories and Scientific Services, TGA.

The specifications have acceptable expiry limits and release limits that allow for the changes observed on storage. All individual degradants of sildenafil and total degradants were limited to the appropriate standard. A degradation product of an excipient was also appropriately limited. There were suitable limits for appearance, sterility, bacterial endotoxins, subvisible particles and extractable volume.

Stability data were provided to support an unopened shelf life of 3 years when stored below 30°C. No other conditions are required.

Biopharmaceutics

The Phase III clinical pharmacokinetic and safety studies were performed with the proposed product or with a second intravenous (IV) solution containing 1 mg/mL of sildenafil with a mannitol base (rather than a glucose base). It was accepted that these two solutions would be bioequivalent.

Study A148-208 was provided comparing this other IV injection formulation to an oral capsule formulation. This study had been previously evaluated by the TGA and it was concluded that the absolute bioavailability of the oral capsule was 41%. It was also accepted that the capsule formulation was relevant to the tablet formulation registered in Australia.

In the draft product information (PI) it is stated that a 10 mg IV dose is predicted to provide exposure of sildenafil and its (*active*) N-desmethyl metabolite and pharmacological effect compared to those of a dose of a 20 mg tablet. Given the above result for study A148-208, and the fact that the amount of N-desmethyl metabolite is 16% and 61% of sildenafil after IV and oral dosing, then the overall levels of the active species for the 10 mg IV injection will be ~12% lower than for the 20 mg tablet.

Advisory Committee Considerations

Given that the product is a simple IV injection and there were no new bioavailability data, details of this submission were not presented to the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality Summary and Conclusions

Approval of application was recommended with respect to chemistry and manufacturing control.

Bioavailability is 100% for this route of administration, but the Delegate should consider that the overall levels of the active species for the 10 mg IV injection will be ~12% lower than for the 20 mg tablet.

III. Nonclinical Findings

Introduction

Revatio is currently registered in Australia for the treatment of PAH at a recommended oral dose of 20 mg three times daily (tds). Sildenafil citrate (oral dosage form) is also registered under the trade name Viagra for the treatment of male erectile dysfunction.

No new nonclinical studies specifically investigating the new dosage form of sildenafil citrate were submitted. This section of the application was primarily based on the nonclinical studies performed in support of the original registration application for sildenafil citrate tablets (Viagra) and for the PAH indication under the trade name Revatio. The primary objective of this assessment was therefore to establish the nonclinical safety and efficacy of sildenafil citrate with the proposed new dosage regimen, particularly with respect to relative exposure levels.

Several relevant repeat dose toxicity studies were resubmitted with this application. Some of these studies involved administration of sildenafil free base and some involved administration of sildenafil citrate; this issue is discussed further under *Relative exposure* below. Three new *in vitro* pharmacokinetic studies have also been submitted as part of the current application, which are discussed under the relevant subheading below.

Pharmacology (Efficacy)

The efficacy of sildenafil in PAH in nonclinical studies was discussed in a previous evaluation report. Briefly, hypoxic pulmonary vasoconstriction in dogs was partially reversed with IV dosing of sildenafil (≥ 1.5 $\mu\text{g/kg}$; the chemical form of sildenafil administered was not specified), with resulting free plasma sildenafil concentrations of ≥ 5 nM (3.3 ng/mL; about 3 times lower than the clinical maximal plasma concentration [C_{max}]). Thus, the available nonclinical efficacy data support the efficacy of sildenafil at the proposed IV dose.

Pharmacokinetics

Three new nonclinical pharmacokinetics studies were submitted with this application, investigating the *in vitro* metabolism of sildenafil in human tissues. Sildenafil was metabolised by human liver microsomes expressing cytochrome P450 (CYP) 3A4 to form a major human metabolite (N,N-de-ethylated sildenafil, or NDE-sildenafil), with a substrate concentration (K_m) value of 21 μM . CYP1A2, CYP2C9, CYP2C19 and CYP2D6 did not mediate the formation of NDE-sildenafil *in vitro*. Clearance of sildenafil by recombinant human CYP3A7, the fetal form of CYP3A4, was about 25 times lower than that of CYP3A4 *in vitro*. Sildenafil did not significantly inhibit the activity of CYP2B6 and CYP2C8 in human liver microsomes *in vitro*.

Relative exposure

Toxicokinetic data were not obtained in the original IV repeat dose toxicity studies for sildenafil; thus direct comparison of relative exposure in animals and humans was not possible. Instead, pharmacokinetic data were obtained following single IV doses of sildenafil free base to rats and dogs, which were used to calculate extrapolated relative exposure in nonclinical toxicity studies. However, limited dose ranging was conducted in IV pharmacokinetics studies in rats (in separate studies), resulting in variable results. The pharmacokinetic data from study DM11 were expected to be the most robust and were used for extrapolation in this species, based on slightly larger group sizes and increased blood sampling. In nonclinical IV pharmacokinetic studies, sildenafil was administered as free base, whereas either the free base form or sildenafil citrate (the registered product) was administered in IV toxicity studies. Given the proposed IV route of administration, differences in bioavailability are not expected for the two different chemical forms; thus, the pharmacokinetics of sildenafil base were considered to be applicable for studies conducted using sildenafil citrate.

Extrapolated exposure levels of sildenafil (area under the plasma concentration time curve [AUC] and C_{1st}) and an active metabolite, NDM-sildenafil (C_{max}), from these studies were compared with exposure data from human PAH patients at the recommended

clinical dose. The proposed clinical IV dose of sildenafil is 10 mg tds, administered by a bolus injection. The clinical pharmacokinetic data were calculated following a single 10 mg bolus dose and AUC based exposure was expressed as the area under the plasma concentration time curve from time zero to 6 hours (AUC_{0-6h}) (the sampling period) and AUC_{0-8h} (extrapolated from the predicted C_{8h} to encompass the dosing interval). To account for AUC based exposure anticipated from thrice daily administration of this dose of sildenafil citrate, the AUC value for the dosing interval was multiplied by three (i.e. $329.7 \text{ ng.h/mL} \times 3 = 989.1 \text{ ng.h/mL}$); this value was used for AUC based exposure calculations. Similar calculations were made for NDM-sildenafil.

As plasma sildenafil concentrations in nonclinical studies were generally at or approaching the lower limit of quantification at the end of each sampling period, direct comparison of AUC values with the clinical AUC, irrespective of time period (that is, 0–8 hours or 0– ∞), was considered appropriate. Results are summarised in Table 1. Exposure margins were also adjusted to account for differences in plasma protein binding of sildenafil in dogs and humans, expressed as free (unbound) sildenafil AUC values. Respective unbound fractions of sildenafil and N-demethylated sildenafil were 0.05 and 0.11 (rats), 0.14 and 0.14 (dog) and 0.04 and 0.05 (human). Doses in [brackets] represent No Observable Adverse Effect Levels (NOAELs) for respective toxicity studies.

Table 1: Relative exposure (AUC and C_{1st} or C_{max}) in nonclinical studies with sildenafil

Species	Sex	Dose (mg/kg/day)	Analyte	Exposure multiple (AUC)		Exposure multiple (C _{1st} or C _{max})	
				Total	Free	Total	Free
Single dose IV pharmacokinetics studies							
Rat	M	1	Sildenafil	0.2	0.3	0.9	1.1
			NDM-sildenafil	NA	NA	0.8	1.8
	F		Sildenafil	0.6	0.7	1.3	1.6
			NDM-sildenafil	NA	NA	0.4	0.8
	M	4	Sildenafil	1.4	1.8	12	15
			NDM-sildenafil	NA	NA	5	10
	F		Sildenafil	5	6	9	12
			NDM-sildenafil	NA	NA	3	6
Dog	M	0.3	Sildenafil	0.5	1.8	0.5	1.8
		1		1.6	5	1.1	4
		0.3	NDM-sildenafil	NA	NA	NA	NA
		1		NA	NA	0.6	1.6
Repeat dose IV toxicity studies (extrapolated data)							
Rat 13 days	M	2.5	Sildenafil	0.9	1.1	7	9
		5		1.8	2.2	15	18
		[10]		[14]	[18]	[116]	[145]
		2.5	NDM-sildenafil	NA	NA	3	6

F	5	Sildenafil	NA	NA	6	13
	[10]		NA	NA	[47]	[101]
	2.5	Sildenafil	3	4	6	7
	5		6	8	12	15
	[10]		[52]	[64]	[94]	[118]
	2.5	NDM-sildenafil	NA	NA	1.7	4
	5		NA	NA	3	8
	[10]		NA	NA	[28]	[59]

Table 1 continued

Species	Sex	Dose (mg/kg/day)	Analyte	Exposure multiple (AUC)		Exposure multiple (C _{1st} or C _{max})	
				Total	Free	Total	Free
Repeat dose IV toxicity studies (extrapolated data)							
Rat 1 month	M	0.5	Sildenafil	0.2	0.2	1.5	1.8
		[2]		[0.7]	[0.9]	[6]	[7]
		4		1.4	1.8	12	15
		0.5	NDM-sildenafil	NA	NA	0.6	1.3
		[2]		NA	NA	[2]	[5]
		4		NA	NA	5	11
	F	0.5	Sildenafil	0.6	0.8	1.2	1.5
		[2]		[3]	[3]	[5]	[6]
		4		5	6	9	12
		0.5	NDM-sildenafil	NA	NA	0.4	0.8
		[2]		NA	NA	[1.4]	[3]
		4		NA	NA	3	6
Dog 14 days 1 month	M/F	[2.5]	Sildenafil	[4]	[14]	[3]	[10]
		5		8	27	6	19
		10		16	54	11	39
		[2.5]	NDM-sildenafil	NA	NA	[1.5]	[4]
		5		NA	NA	3	9
		10		NA	NA	6	17
	M/F	0.5	Sildenafil	0.8	3	0.6	1.9
		2		3	11	2	8
		[4]		[6]	[22]	[4]	[16]
		0.5	NDM-sildenafil	NA	NA	0.3	0.7
		2		NA	NA	1.2	3
		[4]		NA	NA	[2]	[7]

NA = not applicable; NC = not calculated; NDM-sildenafil = N-demethylated sildenafil; NOAELs in toxicity studies are shown in [brackets]

Toxicology (Safety)

No new nonclinical toxicity studies for sildenafil were submitted. Thus, the safety assessment of the IV dose form relies on existing nonclinical data. Repeat dose toxicity studies by the IV route of up to one month duration in rats and dogs were previously conducted. The studies were Good Laboratory Practice compliant and generally adequate. Studies of 13–14 days duration were conducted in each species using sildenafil base and studies of 1 month duration were conducted using sildenafil citrate. Sildenafil was generally well tolerated in both species, with findings generally consistent with its primary pharmacology. Treatment related findings included redness of the ears in both species, an increased incidence of chronic inflammation of the myocardium in male rats and reduced papillary reflex, liquid faeces and increased heart rate in dogs. The clinical significance of the myocardial inflammation in rats was unclear, as similar findings were not observed in oral studies of up to 6 months duration. Exposure (AUC and C_{1st} or C_{max}) to sildenafil and its active metabolite in nonclinical studies at NOAELs was generally greater than exposure in PAH patients at the recommended clinical dose, except for male rats, which showed species specific sex differences in pharmacokinetics.

Local tolerance

The potential for local toxicity of sildenafil by the IV route was assessed following a single intraarterial dose in rabbits (2 mg/mL sildenafil, or 2.5 times greater than the proposed clinical concentration of 0.8 mg/mL) and in the IV repeat dose toxicity studies in rats and dogs (sildenafil concentrations of ≤ 5 mg/mL; 6 times the clinical sildenafil concentration). There were no treatment related findings at the injection site in rats, rabbits or dogs.

Use in children

The IV dose form of sildenafil citrate is indicated for adult patients only.

Nonclinical Summary and Conclusions

No new nonclinical studies specifically investigating the new dosage form of sildenafil citrate were submitted. Thus, the assessment of the nonclinical safety and efficacy of the new dosage form relies on existing data.

Previous *in vivo* primary pharmacodynamic data (IV dosing) for sildenafil are indicative of efficacy in PAH patients at clinically relevant doses.

In vitro metabolism studies in human tissues identified CYP3A4 as the enzyme responsible for formation of an N-de-ethylated metabolite. Sildenafil did not inhibit human CYP2B6 or CYP2C8 activity *in vitro*.

Previous IV repeat dose toxicity studies of up to one month duration in rats and dogs identified effects consistent with the primary pharmacology of sildenafil. Exposure (AUC and C_{1st} or C_{max}) to sildenafil and its active metabolite in nonclinical studies at NOAELs was generally greater than exposure in PAH patients at the recommended clinical dose.

There was no evidence of local toxicity following a single intraarterial injection in rabbits, or repeated intravenous dosing of rats and rabbits, at sildenafil concentrations 3–6 times greater than the concentration of the clinical product.

There were no nonclinical objections to the registration of the IV dose form of sildenafil for the proposed indication.

IV. Clinical Findings

Introduction

The following studies were submitted:

- 3 pharmacokinetic (PK) studies (previously submitted to TGA)
- 1 population PK study (previously submitted to TGA)
- 6 clinical studies (3 of which have been previously submitted to TGA)

Pharmacokinetics

Introduction

The data submitted included data from two intravenous (IV) studies in patients with pulmonary artery hypertension (PAH) comprising a total of 95 patients, three studies of IV administration to healthy volunteers (26 healthy volunteers), one study in patients with ischaemic heart disease (8 patients) and two studies of administration to paediatric patients (42 patients).

Pharmacokinetics in the target population and in healthy volunteers

Four studies of the pharmacokinetics of sildenafil following IV administration were provided. One of these (**study A1481262**) was a pivotal study of the IV bolus administration of 10 mg in patients with PAH. The remaining three studies were of stepwise infusions of sildenafil in patients with PAH (1 study) and three studies in healthy volunteers including an absolute bioavailability study. It is worth noting that two oral studies of sildenafil in the treatment of patients with PAH using doses ranging through 20, 40 and 80 mg three times daily (tds) were included in the data provided. These were **studies A1481140** and **A1481141** which were the pivotal oral studies in the previous marketing application for oral administration of sildenafil in patients with PAH.

Study A1481262

Study A1481262 was an open, single dose pivotal study to assess the safety, tolerability and pharmacokinetics of an IV bolus dose 10 mg of sildenafil in patients with PAH who were stable on and tolerated oral sildenafil 20 mg tds for at least one month. It was intended to study 12 patients but due to difficulties in recruiting only 10 patients completed the study. A signal indicating possible problems with hypotension was considered to exist if three or more patients developed hypotension during the study.

All subjects attended the clinic on the day of dosing having omitted their morning oral dose of sildenafil. The subjects received an IV dose of 10 mg sildenafil (12.5 mL of a 50 mL vial). Sildenafil was given as a single IV bolus injection into an antecubital vein. Sildenafil citrate was supplied in 50 mL vials (0.8 mg per mL). The mean age of the subjects was 59.5 (standard deviation [SD]; 11, range 46-76) years (5 male and 5 female) and 8 of the 10 subjects were receiving bosentan, a treatment for PAH that increases the clearance of sildenafil by about 60%. The pharmacokinetic data derived from the study are summarised in Table 2.

Table 2: Pharmacokinetic parameters derived from a bolus intravenous dose of sildenafil 10 mg to 10 patients with pulmonary artery hypertension (from study A1481262)

PK parameter	Mean	SD	Min-max
Clearance (L/h)	32.19	12.31	18.7 – 60.3
C _{max} (ng/mL)	240.34	108.61	55.4 – 433.0
T _{max} (hr)	0.083	-	0.08 – 0.13
AUC ₀₋₈ (ng.h/mL)	348.2	117.9	166-534
Vd (L)	137.25	52.02	58.1 – 222.0
T _½ (hr)	3.24	1.72	1.53-6.96

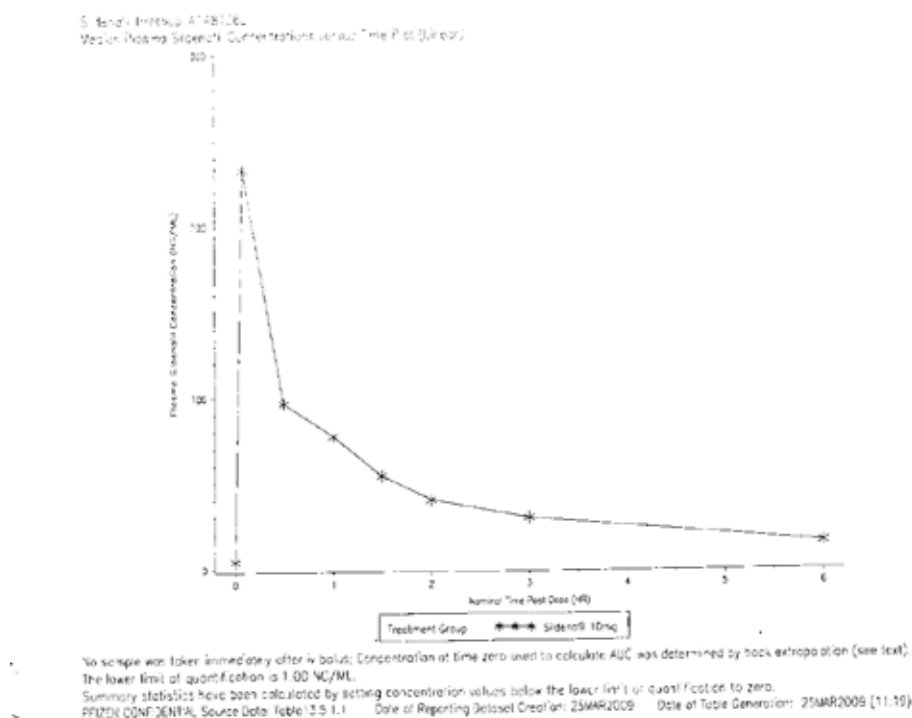
T_{max}: time to maximal plasma concentration

Vd: volume of distribution

T_½: half-life

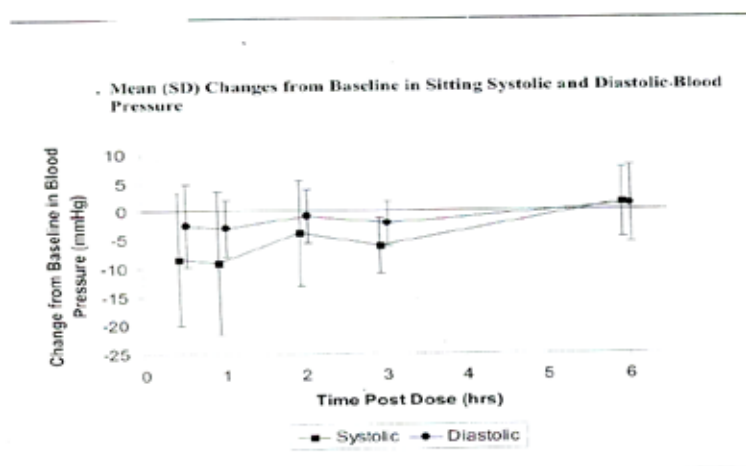
There appears to be what must be an error in the plasma levels that were reported in the tables provided by the sponsor. The pre-dose mean concentration of sildenafil is indicated to be 248.4 ng/mL compared with the C_{max} mean value of 213.3 ng/mL. This error does not appear to be replicated in the graph of the pharmacokinetic results for sildenafil that is presented in Figure 1. The evaluator assumed that the value should have been 24.8 ng/mL. This was resolved with the sponsor. The C_{max} value is of greatest interest in this study as the major concern in administering sildenafil as an IV bolus is that a high C_{max} with attendant hypotension may occur. The maximum C_{max} recorded (433 ng/mL) was well within the range shown to be safe in previous IV studies of sildenafil infusions (**Study A148-203**). The changes in blood pressure were relatively small with mean reductions one half and one hour post dose of around 10 mmHg. No episodes of hypotension or dizziness were encountered. Changes in blood pressure are presented in Figure 2.

Figure 1: Plasma concentration versus time graph for sildenafil 10 mg given as a bolus intravenous injection in study A1481262.



Note that no sample was taken immediately after the IV bolus. Concentration at time 0 used to calculate AUC was determined by back extrapolation.

Figure 2: Changes in blood pressure following an intravenous bolus injection of sildenafil 10 mg in study A1481262.



A flaw in the study design was that the first blood pressure post dose was taken at 30 minutes rather than immediately following the IV bolus of sildenafil. Several blood pressures should have been taken at intervals during the first 30 minutes following

administration when the plasma concentrations of sildenafil would have been at their highest. This flaw is not a major deficit in terms of the value of the study.

Although the numbers in this study were small and 8 of the patients were receiving bosentan, the C_{\max} values were in the range previously well tolerated in other studies. For example, the C_{\max} recorded following IV infusions of 80 mg of sildenafil had a mean value of 1822 ng/mL (Study A148-203) compared to maximum recorded in this study of 433 ng/mL. Pharmacokinetic modelling done on this and other studies (**Study A1481024**, Study A148-203) indicated that, as would be expected, the C_{\max} would not be significantly altered by the presence or absence of bosentan. (Bosentan would be more likely to increase the first pass extraction and increase clearance).

It would have been preferable for this study to have had a larger number of subjects and to record blood pressures at earlier times closer to the C_{\max} .

Study A1481024

Study A1481024 was a study of IV stepwise infusions of sildenafil targeting plasma concentrations of 100, 300 and 500 ng/mL with the infusion given over 20 minutes at each target level. The age range varied depending upon the group but was around means of 40 to 55 years of age. There was an extension phase of the study where the target plasma concentrations were 10, 50 and 100 ng/mL per mL. In the initial phase of the study all subjects received nitric oxide inhalation therapy. In the extension phase 66% received nitric oxide inhalation therapy. The study investigated 45 patients with PAH (primary or secondary) of which 6 received placebo, 34 patients with pulmonary venous hypertension secondary to congestive heart failure of which 9 received placebo and 6 patients with hypoxic pulmonary artery hypertension due to obstructive airways disease, all of whom received active treatment. A range of haemodynamics (as well as plasma sildenafil levels) was studied including pulmonary vascular resistance. The pharmacokinetic results of the study were limited except for showing that the selected infusion rates approximately achieved the desired steady state plasma concentrations (no further pharmacokinetic data were presented). The study found that the maximum effect in reducing pulmonary vascular resistance occurred with a dose around 100 ng/mL of sildenafil. This study was not of major relevance to the current marketing application as the sildenafil dose was given as a 20 minute IV infusion rather than the IV bolus proposed as the mode of administration for this marketing application.

Study A148-208

Study A148-208 was an absolute bioavailability study of 50 mg of IV sildenafil given over 50 minutes compared to 50 mg given orally in 12 healthy volunteers. The study was an open label randomised two way crossover study of a single dose of 50 mg sildenafil given orally (2x25 mg capsules) and a 50 mg intravenous dose given as 50 mL of a 1 mg per mL solution of sildenafil infused at 1 mL per minute. Twelve healthy male subjects aged 18-42 years received IV or oral sildenafil in a random order with 6 subjects in each treatment order. The mean age of the subjects receiving oral sildenafil first was 23 years while the mean age of those receiving the intravenous solution first was 27 years. The subjects ranged in weight from 59-87kg. Each study day was separated by a wash out period of at least 10 days.

The plasma vs concentration time curves following oral and intravenous administration are presented in Figure 3. The results for pharmacokinetic parameters from the study are presented in Table 3.

Figure 3: Plasma concentration versus time curves for oral and intravenous sildenafil 50 mg for study A148-208.

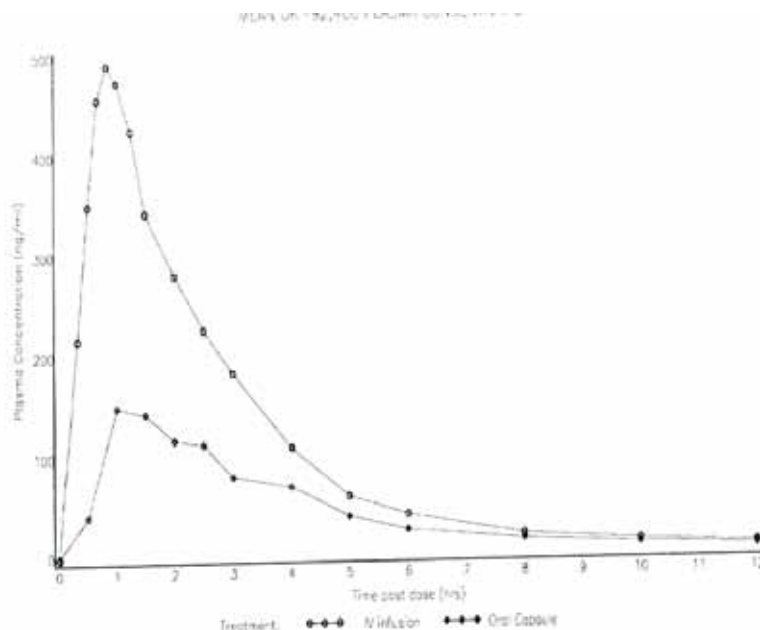


Table 3: Pharmacokinetic parameters following an oral or intravenous dose of sildenafil 50 mg for study A148-208

PK parameter	IV	Oral	Ratio (90% confidence intervals)
AUC (ng.h/mL)	1291.07	529.91	41.0% (35.6% -47.3%)
C _{max} (ng/mL)	530.78	159.53	30.1% (26.8% -33.8%)
PK parameter	IV	Oral	Difference between means (90% confidence intervals)
K _{el} (hr)	0.18	0.17	-0.006 (-0.02 - 0.008)
T _{max} (hr)	0.73	1.46	0.73 (0.44 - 1.02)

The absolute bioavailability of sildenafil 50 mg following oral administration measured as the ratio of the area under the curves from zero to infinity was 41.0% with 90% confidence intervals (CI) of 35.6% to 47.3%. As would be expected the C_{max} was substantially higher following IV compared to oral administration. As would also be expected the T_{max} was substantially later following oral than following IV administration but the elimination half lives were essentially the same. This was an adequately performed study that demonstrated that the absolute bioavailability of oral sildenafil is slightly less than 50% of the same dose given IV. As the pharmacokinetics of sildenafil at doses less

than 50 mg have previously been shown to be essential linear (Study A148-203) these results support the use of an IV dose (that is, 10 mg IV tds) that is 50% of the usual marketed oral dose of sildenafil in pulmonary artery hypertension of 20 mg tds. IV and oral sildenafil 50 mg were well tolerated with only mild symptoms reported, the most common of which was headache (3 patients with treatment related adverse events on the IV infusion compared to 4 on the oral capsule).

Study B148-203

Study B148-203 was a pharmacokinetic study in 8 male healthy volunteers of single IV doses of 20, 40 and 80 mg of sildenafil given as a 2 mL per minute infusion over 40 minutes. It was a single blind four way crossover dose escalation study with randomly inserted doses of placebo. Each dose was separated by a wash out period of at least 7 days and escalation to the higher dose was dependant on toleration of the previous dose.

The subjects' age ranged from 19-30 years and their weights were 65-81 kg. The results of the study are presented in Table 4.

Table 4: Pharmacokinetic parameters derived from study A148-203.

Sildenafil dose	C_{max} (ng/mL)	AUC_t (ng.hr/mL)	T_{max} (hr)
20 mg	341 ± 95	725 ± 134	0.67 ± 0.09
40 mg	865 ± 250	1590 ± 352	0.58 ± 0.09
80 mg	1850 ± 356	3758 ± 650	0.69 ± 0.06

Note- half life was not presented.

AUC_t = area under the plasma concentration versus time graph measured to the last sampling time.

The maximum individual plasma concentration achieved at the 80 mg dose was 2557 ng/mL. The linearity of pharmacokinetics based on the ratio of the AUC had a proportionality term of 1.19 (90% CI 1.10-1.36). This is not clinically significant. No subjects discontinued treatments because of adverse events. Rash occurred in one patient while headache occurred in 3, 4 and 5 out of the 8 volunteers respectively for the 20 mg, 40 mg and 80 mg doses of sildenafil. Dizziness occurred in 4 and 2 patients respectively out of 8 at the 40 and 80 mg doses. Apart from demonstrating that plasma concentrations following IV administration of sildenafil were well above the C_{max} of 10 mg IV as a bolus injection and were well tolerated, this study was not of major relevance to the current marketing application as the sildenafil dose was given as a 40 minute infusion rather than as an IV bolus.

Study A148-215

Study A148-215 was an open, parallel group study that investigated the absorption, excretion and metabolism of radio labelled sildenafil in 6 healthy volunteers, 3 of who received 25 mg sildenafil infused IV over 25 minutes. The absorption of sildenafil was 92%. The study was of little value to this application as it was very small, studied 25 mg rather than 10 mg and involved an infusion rather than an IV bolus injection.

Population PK Studies

A population pharmacokinetic and pharmacodynamic analysis was performed on Study A1481024 in the 85 patients in this study that suffered from pulmonary artery hypertension. This analysis found that the median effective dose (EC₅₀) for IV sildenafil for systolic pulmonary artery pressure reduction was 14.5 mg with 90% CI from 7.3 to 35.0. This analysis was of little relevance as it did not address the effect of IV administration as a bolus dose.

A two compartment pharmacokinetic model of study A148-203 in which normal volunteers received infusions of sildenafil 20, 40 or 80 mg given over 40 minutes predicted that the C_{max} of IV 10 mg given as a bolus would be 203 ng/mL. This is close to the actual value of 240 ng/mL recorded in the pivotal IV bolus study A1481262. This analysis is of some value as the plasma sampling times in study A1481262 were limited.

Another pharmacokinetic modelling analysis was performed to predict the pharmacokinetic profile at steady state of sildenafil given IV from studies A148-203, A148-208 and **A148-211** (this last study was not submitted for evaluation). This analysis demonstrated that bosentan increases the clearance of sildenafil and reduces the AUC by approximately 63%. This is of relevance as 8 of the 10 patients in the pivotal IV bolus Study A1481262 were receiving bosentan. The model predicted that there would be no significant impact upon the C_{max} , which is what would be expected as the C_{max} following an IV bolus would not be expected to be greatly affected by clearance. Furthermore, the pharmacokinetic profile at steady state was predicted to vary little from that observed in study A1481262.

A further population pharmacokinetic modelling analysis investigated the potential impact of the concomitant use of CYP3A4 inhibitors on the pharmacokinetics of sildenafil 10 mg given as a bolus injections and in particular, whether accumulation may occur that would increase the value of the C_{max} following repeated IV injections. The analysis found that CYP3A4 inhibition primarily increased bioavailability of oral sildenafil. While a reduction in clearance was predicted this was not accompanied by a major change in accumulation and the predicted C_{max} following an IV bolus injection of 10 mg remained in the concentration range previously shown to be safe.

Evaluators overall conclusions on pharmacokinetic studies

The studies submitted demonstrate that the IV bolus injection of sildenafil at a dose of 10 mg produces a C_{max} value well below values achieved in other studies that were well tolerated. This C_{max} value is very unlikely to be affected by the concomitant administration of bosentan or CYP 3A4 inhibitors. Accumulation of sildenafil when given three times a day would be very unlikely to occur and three times daily administration of sildenafil IV would be expected to produce essentially the same plasma profile as three times daily oral sildenafil at a dose of 20 mg as is currently approved for marketing.

Pharmacodynamics

Study A1481024

Limited new data were presented except for the small amount of pharmacodynamic monitoring included in the pharmacokinetic studies and data from study A1481024. This study was described above and was a small study in patients with ischaemic heart disease. A summary of the changes in pulmonary vascular resistance in the initial and extension phases of study A1481024 are presented in Table 5.

Table 5: Changes in pulmonary resistance (dyne.sec/cm⁵) in study A1481024 for patients with pulmonary artery hypertension (mean \pm SE)

Initial study	Baseline (post NO)	100 ng/mL	300ng/mL	500ng/mL
Sildenafil (n= 10)	954 \pm 145	736 \pm 333	788 \pm 120	770 \pm 140
Placebo (n = 3)	841 \pm 239	669 \pm 230	709 \pm 238	656 \pm 301
Extension study	Baseline	10 ng/mL	50 ng/mL	100 ng/mL
Sildenafil (n = 9)	1148 \pm 229	1031 \pm 178	942 \pm 167	864 \pm 160
Placebo (n = 3)	1296 \pm 242	1356 \pm 263	1398 \pm 254	1341 \pm 241

NO = Nitric oxide.

Comparisons between sildenafil and placebo are limited by the small number of patients on placebo. However, the data appear to indicate that the most of the reduction in pulmonary vascular resistance occurs at 100 ng/mL.

Study A148-301

Study **A148-301** was an investigation of the effects of sequential and cumulative infusions of IV sildenafil at doses of 5,10, 20 and 40 mg each given over 15 minutes. This open, uncontrolled study involved 8 male patients with ischaemic heart disease of mean age 60 (range 52-70) years. Haemodynamics were measured at baseline and following the sildenafil infusions at rest and following 4 minutes of bicycle exercise using a Swan-Ganz central catheter. The results of the study are presented in Table 6.

Table 6: Results of haemodynamics derived by Swan-Ganz catheterization from study A148-301

Means \pm SD	At rest	At rest	After exercise	After exercise
	Baseline	Sildenafil	Baseline	Sildenafil
PAOP (mmHg)	11.0 \pm 4.8	7.8 \pm 4.7	36.0 \pm 13.7	27.8 \pm 15.3
Mean PAP (mmHg)	17.7 \pm 3.9	13.3 \pm 4.1	39.4 \pm 12.9	31.7 \pm 13.2
Mean RAP (mmHg)	5.7 \pm 3.7	4.1 \pm 3.7	-	-
Systolic SAP (mmHg)	155 \pm 17	143 \pm 17	200 \pm 37	188 \pm 30
Diastolic SAP (mmHg)	74 \pm 8.3	63 \pm 15	85 \pm 10	80 \pm 9
Cardiac output (l/min)	6.6 \pm 1.6	5.2 \pm 0.4	11.5 \pm 2.4	10.2 \pm 3.5
Heart rate (beats/min)	64 \pm 10	70 \pm 14	102 \pm 12	99 \pm 20

PAOP = pulmonary artery occlusion pressure, PAP = pulmonary artery pressure, RAP = right atrial pressure, SAP = systemic arterial pressure.

The value of this study was limited because it studied patients with ischaemic heart disease rather than patients with pulmonary artery hypertension, it used IV infusions rather than an IV bolus injection and the doses were well in excess of the 10 mg IV intended for marketing. However, the results do indicate that high doses of sildenafil well in excess of the dose intended for marketing are well tolerated without the occurrence of significant or symptomatic hypotension.

Overall these data from the haemodynamic and pharmacokinetic studies indicate that excessive blood pressure or pulmonary vascular resistance reductions do not occur with plasma concentrations of sildenafil that are achieved following the IV bolus administration

of sildenafil at a dose of 10 mg and would be unlikely to occur with repeated administration of sildenafil 10 mg IV as a bolus dose given three times daily.

Efficacy

No new efficacy data were presented.

Safety

Introduction

While a considerable amount of data were presented concerning the safety of sildenafil given IV, the main safety concern is the effect on blood pressure and other associated haemodynamic effects including pulmonary and systemic vascular resistance when the drug is given as a bolus injection and a rapid rise and fall in plasma concentrations occur. Only one study with 10 patients addressed this issue (Study A1481262). In all of the other studies submitted for evaluation sildenafil was given as a slow IV infusion of variable duration.

Patient exposure

The data submitted included data from two IV studies in patients with pulmonary artery hypertension comprising a total of 95 patients, three studies of IV administration to healthy volunteers (26 normal volunteers), one study in patients with ischaemic heart disease (8 patients), two studies of administration to paediatric patients (42 patients) and two studies of oral administration in 542 patients with pulmonary artery hypertension.

Adverse events

In study A1481262 (10 patients with pulmonary artery hypertension who received a single IV bolus dose of 10 mg of sildenafil) two subjects had falls in systolic blood pressure of greater than 20 mmHg in the first hour post dose but these were not symptomatic. Three subjects reported adverse events (AEs) that were considered to be treatment related. One suffered flatulence while two reported flushing. One patient died but this was 6 days after the IV administration and the death was due to ventricular fibrillation and not considered to be related to study medication.

In study A1481024 (85 patients with pulmonary artery hypertension of various causes who received 20 minute IV infusions of sildenafil targeting plasma concentrations of 100, 300 and 500 ng/mL or 10, 50 and 100 ng/mL in the extension phase), 24 patients experienced a total of 40 adverse events of which 17 events in 12 patients were considered by the investigators as being treatment related. Most adverse events were mild. The most common adverse events considered to be treatment related were four reports of vasodilation and two each of hypotension, headache and nausea. Five adverse events were considered to be severe, three of which were considered to be treatment related. These were severe hot flushes, severe nausea and severe headache. One serious adverse event, bacteraemia, was reported but not considered to be treatment related. One subject died 40 days after the study from pneumonia that was first reported 15 days after the study. This was not considered to be treatment related. Fifteen patients withdrew from the study but only three because of adverse events (two of which were considered treatment related, severe nausea and hypotension). It is unclear from the data whether the occurrence of treatment related adverse events was dose related. No laboratory abnormalities occurred that were considered treatment related. No reported laboratory abnormalities were considered to be clinically significant.

In study A148-208 (a randomised crossover trial in 12 healthy volunteers who received 50 mg of sildenafil IV over 50 minutes and 50 mg orally for the determination of absolute bioavailability) seven of the subjects reported adverse events during or following the IV

infusion and 8 reported adverse events following oral administration. Most adverse events were considered to be mild. The most commonly reported adverse event was headache (4 reports). There was one episode of haemorrhage at the site of the IV line insertion. There were 3 adverse events that were considered to be treatment related during or following the IV infusion and 4 following oral administration. In the IV infusion arm of the study there were 2 episodes of mild headache and one of mild vasodilation and following oral administration there were 2 episodes of mild headache, one of moderate headache and one of moderate nausea. There were no severe adverse events and all 12 subjects completed the study. There were no laboratory abnormalities that were considered to be treatment related or to be of clinical significance.

In study A148-203 (a crossover study of single IV doses of sildenafil 0, 20, 40 and 80 mg given over 40 minutes to 8 healthy male volunteers) there were 4 adverse events on placebo, 5 on 20 mg, 6 on 40 mg and 8 on 80 mg. The corresponding numbers of adverse events thought to be treatment related were 2, 4, 5 and 6. Most adverse events were mild except for one rash and one moderate headache. Headache was the most common adverse event with vasodilation and dizziness also reported. All subjects completed the study and there were no serious adverse events. There were no laboratory abnormalities that were considered to be of clinical significance or to be treatment related. The occurrence of adverse events was clearly dose related but it should be noted that the doses studied were well in excess of the 10 mg dose intended for marketing.

In study A148-301 (an open study of cumulative IV infusions of 5, 10, 20 and 40 mg over 15 minutes each in 8 patients with ischaemic heart disease), only one adverse event was reported (severe back pain) and this was considered by the investigator not to be of clinical significance. There were 7 clinically significant laboratory abnormalities (5 haematological, 2 gamma-glutamyl transferase [GGT]) none of which were considered to be treatment related. There were no serious adverse events and all of the patients completed the study.

In study **A1481134** (a placebo controlled trial of variable IV doses with target plasma concentrations of 0, 40, 120 and 360 ng/mL with infusion durations of 24 to 72 hours following a 5 minute infusion loading dose in 17 children 0-17 years), 15 patients reported 45 adverse events. These were principally pulmonary hypertension and no adverse event was considered to be treatment related. There were 3 discontinuations, one due to pulmonary hypertension, one withdrawn prior to randomisation and one due to lack of efficacy. There was one death due to pulmonary hypertension. There were no laboratory test abnormalities that were considered to be treatment related.

This study was of limited value for assessing the safety of sildenafil 10 mg IV as a bolus injection in adults as it was performed in young children and prolonged IV infusions were studied.

In study **A1481157** (an open placebo controlled study in 36 infants with persistent pulmonary hypertension of the newborn involving a loading dose of IV sildenafil followed by a 48 to 168 hour infusion with a target plasma concentration of 150 ng/mL), 20 patients had adverse events but only 5 were considered to be treatment related. There were 4 severe adverse events including one death but these were not considered to be treatment related. Four subjects withdrew due to adverse events. None of these were considered to be treatment related. Most of the adverse events reported were mild. The treatment related adverse events were hypotension (3), labile blood pressure (1) and patent ductus arteriosus (1). The most commonly reported adverse event was hypotension. Laboratory abnormalities were not reported.

This study was of also limited value for assessing the safety of sildenafil 10 mg IV as a bolus injection in adults as it was performed in young children and prolonged IV infusions were studied.

In study **A148-215** (an open parallel group study of radio labelled 50 mg oral given to 3 healthy volunteers compared to 25 mg given as a 50 minute infusion to 3 healthy volunteers), 5 of the 6 subjects reported adverse events, 3 of whom received IV sildenafil and 2 of whom received oral sildenafil. All of the adverse events were considered to be mild except for one episode of painful legs that occurred 15 hours after receiving oral sildenafil. The adverse events (all cause) were back pain, nausea and penile erection. Three adverse events were considered to be treatment related and 2 of these occurred following IV dosing. These were mild nausea and penile erection. The remaining treatment related adverse event was the leg pain following oral dosing. There was one serious adverse event, haematuria, which occurred 15 days after dosing and was not considered to be treatment related. There were no laboratory abnormalities.

Postmarketing experience

There were ten studies identified in which IV infusions of sildenafil had been used in pulmonary hypertension but generally in forms of pulmonary hypertension other than primary pulmonary hypertension. Most of these were small (maximum number of 13 patients) investigator initiated studies. All used doses greater than 10 mg. All of these studies used infusions of sildenafil rather than bolus injections. Most of the studies did not report adverse events and the remainder, except one, reported that no adverse events occurred. One study reported flushing that was mild.

Overall conclusions on clinical safety

The data presented indicate that IV sildenafil is well tolerated, even at doses well in excess of that which is intended for marketing. The most common side effects are headache and flushing which are generally mild. These data principally come from studies that used IV infusions and the amount of data concerning the safety of an IV bolus dose is very limited. However, the maximum plasma concentrations achieved following an IV bolus dose of 10 mg are well within the range shown to be well tolerated in IV infusion studies of higher doses. The incidence and nature of side effects that occur following IV administration are similar to those observed following oral administration (Study A148-208). No problems were observed nor would be expected in changing from oral to IV therapy (in those patients who have tolerated long term oral therapy) nor would it be expected that there would be problems in changing from IV to oral therapy.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

Is there an error in the baseline plasma level in Study A1481262?

Pharmacodynamics

Will any data become available on the pharmacodynamics (in addition to blood pressure data and including pulmonary vascular resistance) for IV bolus injections of sildenafil 10 mg? Will data become available for blood pressure around the time of the C_{max} following IV bolus doses of sildenafil 10 mg as the first blood pressure measurement in study A1481262 was not made until 30 minutes after drug administration?

Safety

Will more data concerning the safety of sildenafil given as a bolus injection become available?

Clinical Summary and Conclusions**Clinical aspects**

Sildenafil is safe and well tolerated over a wide range of doses including up to 80 mg IV and at plasma levels substantially higher than that achieved by the IV bolus administration of 10 mg. All studies used continuous IV infusions of sildenafil except for the one study in 10 patients with pulmonary artery hypertension where an IV bolus dose of 10mg was administered. The only significant concern in administering sildenafil as an IV bolus rather than a continuous infusion is that the rapid rise in plasma levels associated with bolus administration may produce hypotension. The only study to address this concern was study 1481262 in 10 patients with pulmonary artery hypertension where blood pressures were not measured until 30 minutes after drug administration. This is a defect in the study design, as blood pressures should have been measured frequently around the time of the C_{max} . However, no significant episodes of hypotension occurred, at least not significant enough to produce symptoms of dizziness or lightheadedness. While a larger study with 20-30 patients with earlier and more frequent measurement of blood pressure would have been preferable, the evaluator believed that the data were acceptable, particularly considering the fact that plasma levels of sildenafil well in excess of those achieved by a bolus injection of 10 mg have been shown to be safe. It is noteworthy that the EU in their recommendations to the sponsor concerning the requirements for registration of the product only recommended a study in 12 patients.

A comparison of the populations studied in the IV studies and those in the oral pivotal studies that supported the current marketing approval deserves special comment. These oral studies were study A1481140 and study A1481141. A comparison of baseline demographic data for these studies with the pivotal IV study A1481262 and the supportive study A1481024 are presented in Table 7.

Table 7: Comparison of oral and main intravenous studies

Study no., no. of patients (N)	A1481262 N = 10	A1481024 N = 41 (10 placebo)	A1481140 N = 277	A1481141 N = 247
Age (years)	59 ± 11 (46-76)	48 (male) 61 (female) (42-57 male) (41-71) female) initial study	47 ± 13 (19 – 78) for 20 mg dose	48 ± 13 (20-75) for sildenafil group
Gender	50% male	28% male	25% male	20% male
PAH class or Pressure (mmHg)	Class III	PAP ³ 25 mmHg (Class not given)	58% of 20 mg dose Class III	90% Class II or III (no breakdown)
Concomitant therapy for PAH	80% on bosentan	Initial phase 100% received NO, extension phase 66% received NO.	None	epoprostenol
Weight (kg)	81 ± 17 (49-104)	Various depending on group (44-130)	71 ± 17 (41-103) for 20 mg dose	73 ± 20 (38-127)
Ethnicity	100% White	90% White (whole study)	59% White (20 mg dose)	78% White (sildenafil)
Sildenafil dose	10 mg IV	Initial study: stepwise IV infusions targeting plasma concentrations of 100, 300 and 500 ng/mL. Extension study stepwise IV infusions targeting 10, 50 and 100 ng/mL.	Placebo (n=70) 20 mg tds (n=69) 40 mg tds (n=67) 80 mg tds (n= 71)	Placebo (n= 113) 80 mg tds (n=134).

PAH = pulmonary artery hypertension. PAP = pulmonary artery hypertension.

Study A1481024 was complicated as there was an initial phase in which a higher dose of sildenafil was given along with nitric oxide and an extension phase where 9 patients received nitric oxide while 14 did not receive nitric oxide (NO).

It can be seen from Table 7 when comparing the demographics of the small but pivotal study A1481262 with the 20 mg tds group of the pivotal oral study A1481140 that the patients in the IV study were slightly older and there were a greater proportion of males. In addition, they were of slightly greater body weight and all of the subjects were White as opposed to 59% being White in the oral study. Most importantly 8 out of 10 patients in the IV study were receiving bosentan compared to none in the oral study. The issue of the relevance of the use of bosentan in the pivotal study of pharmacokinetics has already been addressed. All of the patients in the pivotal IV study A1481262 had pulmonary artery hypertension Functional Class III compared to 40 patients in the pivotal oral study A1481140. The evaluator believed that the similarities between the patients in the pivotal oral study A1481262 and the pivotal oral study A1481140 are sufficient to conclude that the IV study examined a similar population for study particularly with respect to approving the IV formulation for patients in whom the currently marketed oral formulation at a dose of 20 mg tds oral is indicated.

A comparison between the pivotal IV study A1481262 and the oral study A1481141 is less relevant as the oral study used 80 mg tds in all patients (as opposed to the 20 mg tds which has marketing approval) and all of the patients received epoprostenol. In addition, it is unclear from the report of this study how many patients were Functional Class III as it is only stated that 90% of the population were either Functional Class II or III.

Comparisons between the supportive IV study A14811024 and the two oral studies A1481140 and A1481141 are of relatively little relevance as study A1481024 used IV infusions of sildenafil rather than an IV bolus injection, the doses were different to that intended for marketing and the population was selected on the basis of their pulmonary artery pressure (³ 26 mmHg at rest) rather than their functional class.

Benefit/risk assessment

Benefits

There is a risk that the abrupt cessation of sildenafil when used for the treatment of pulmonary artery hypertension in patients who temporarily cannot take oral medication may lead to a worsening of their condition. This is particularly a concern in patients who are undergoing major surgery where there is a risk of a pulmonary artery hypertensive crisis. The availability of an IV formulation of sildenafil meets a currently unmet need for a way of continuing therapy in patients who are temporarily unable to continue oral therapy.

Risks

The risks associated with IV therapy with sildenafil are low as the incidence and nature of adverse events appear to be no greater than with oral therapy, even at doses well in excess of that intended for marketing. Further data on the haemodynamics of an IV bolus dose as opposed to IV infusions would be of some value in assuring that the risks of an IV bolus dose are low.

Balance

Although further data in a larger number of patients of the haemodynamics and safety of an IV bolus injection of sildenafil would be of value, on balance considering the safety data available and the unmet need for a method of continuing sildenafil therapy in patients temporarily unable to continue oral therapy, the evaluator believed that the potential benefits outweigh the small risks.

Conclusions

The evaluator believed that the availability of an IV formulation of sildenafil would rectify a significant unmet demand and that in the hands of a specialist physician experienced in the management of PAH would be acceptably safe. He recommended approval of the application. However, IV sildenafil should only be administered to patients unable to take oral therapy and who have tolerated and responded to stable oral therapy. IV sildenafil should not be used to initiate therapy. IV sildenafil should only be administered by a physician who is experienced in the management of PAH.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The ongoing safety concerns and the pharmacovigilance activities associated with each as specified by the sponsor are shown in Table 8.

Table 8: Ongoing safety concerns and proposed pharmacovigilance actions

Risk	Safety concern	Pharmacovigilance Actions
Identified risk	Nitrate interaction	
Potential risks	Epistaxis/bleeding events	Enhanced Pharmacovigilance (DCA) Data from ongoing clinical studies · Paediatric: A1481156. · Adult: A1481243; A1481244
	Hypotension	Enhanced Pharmacovigilance (DCA) Revatio hypotension PhV monitoring program Data from ongoing clinical studies · Paediatric: A1481156. · Adult: A1481243; A1481244; A1481262
	Non-arteritic anterior ischaemic optic neuropathy. (NAION)	Enhanced Pharmacovigilance (DCA) Data from ongoing clinical studies · Paediatric: A1481156. · Adult: A1481243; A1481244
	Medication errors associated with the use of the 50 ml vial	Not applicable to the Australian application.
	Deafness/hearing loss	Enhanced Pharmacovigilance (DCA) Data from ongoing paediatric clinical study A1481156.
	Risk related to anti-platelet effects in the presence of a NO donor	Enhanced Pharmacovigilance (DCA)
	Potential drug interactions: epoprostenol, bosentan, iloprost, ambrisentan	Safety data from ongoing study of sildenafil and bosentan: A1481243
Missing or limited information	Paediatric population	Enhanced Pharmacovigilance (DCA) Data from ongoing paediatric clinical study A1481156.
	Long-term ocular safety	Enhanced Pharmacovigilance (DCA) Data from ongoing clinical studies · Paediatric: A1481156. · Adult: A1481243; A1481244
	Pregnancy	Enhanced Pharmacovigilance (DCA) Data from ongoing clinical study of sildenafil in women with pre-eclampsia: A1481206
	Renal Impairment	Enhanced Pharmacovigilance (DCA)
	Cardiovascular safety	Enhanced Pharmacovigilance (DCA) Data from ongoing clinical studies · Paediatric: A1481156. · Adult: A1481243; A1481244
	Long-term mortality	Data from ongoing paediatric clinical study A1481156

DCA: Data Capture Aid

Proposed pharmacovigilance activities

The sponsor proposed enhanced pharmacovigilance (PhV) by way of a 'Data Capture Aid' (DCA) for of the identified safety concerns. The DCA is a prompt for the gathering of supplementary data when at least one of the adverse events (AE) is an identified trigger.

There were no specific current or planned studies proposed as PhV activities specific to the IV formulation. The proposed PhV activities identified by the sponsor are summarised in Table 8.

The Revatio hypotension PhV monitoring program was proposed by the sponsor in the EU in response to the Committee for Medicinal Products for Human Use (CHMP) concern regarding one of the subjects in the IV study who experienced an asymptomatic drop in systolic blood pressure >30 mmHg in the context of relatively low exposure of IV bolus sildenafil in clinical trials. The sponsor outlined a pharmacovigilance monitoring tool to assess the potential risk for hypotension and related problems consisting of a Data Capture Form (DCF). The DCF will be incorporated with each vial of Revatio solution for injection. This would allow obtaining a definite number of users and a number of events (that is, cases of hypotension). In combination with the pharmacovigilance monitoring of hypotension and related problems, an educational program would be implemented aimed at informing pharmacists and physicians that every patient receiving Revatio solution for injection should have the appropriate pharmacovigilance form filled out.

The sponsor indicated it intends to only commercialise the 12.5 mL vial size in Australia and stated that the PhV and risk minimisation relevant to the 50 mL vial will not apply.

Risk Minimisation Activities

The sponsor proposed routine risk minimisation strategies for all the important potential risks and missing information items.² Additional risk minimisation proposed for medication errors for the 50 mL vial (controlled distribution and an educational program for health care providers) were not considered relevant by the sponsor for this application as the intention is to only commercialise the 12.5 mL vial size in Australia. For the risk of hypotension the sponsor's assessment was that routine risk minimisation activities are not sufficient and as such an educational program is proposed aimed at informing pharmacists and physicians that every subject receiving Revatio solution for injection should have the appropriate pharmacovigilance form filled out. This form documents underlying disease(s), cardiovascular history, concomitant medications, baseline blood pressure and provides a check box to record whether the subject experienced clinically important hypotension and related problems.

The OPR evaluator agreed that it was acceptable that risk minimisation strategies relating to potential for medication errors with the 50 mL vial do not need to be implemented in Australia. It was, however, recommended that the sponsor introduce the component of the educational material (DCF) pertaining to the Revatio hypotension PhV monitoring program as part of the risk minimisation activities for the hypotension risk. It was also recommended that the DCF be provided to the OPR for review and approval along with an outline by the sponsor of how the program will be implemented and monitored.

The OPR evaluator also made comments with respect to the proposed product information but these are beyond the scope of this AusPAR.

Conclusion

It was recommended to the Delegate that once RMP amendments and additions are agreed to and the RMP is accepted, that a condition of registration be that the sponsor provides an updated RMP or an annex to the EU-RMP outlining the specific Australian differences, at

² Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

the time of submission of the next PSUR. The OPR evaluator also made the following recommendations to the Delegate:

- The sponsor should update the nonclinical cardiovascular safety section of the RMP to include the findings of myocardial inflammation in rats and provide a conclusion regarding any potential for an associated toxicological hazard in humans.
- While sponsor states that the 50 mL vial is not intended to be marketed in Australia and hence the RMP surrounding the potential for medication errors with the 50 mL vial (for example, accidental overdose) do not apply, the application is not specific to a particular vial size and therefore the sponsor should provide a commitment to implementing this aspect of the RMP if the 50 mL vial is marketed in Australia at a later date.
- The sponsor should implement the Revatio hypotension PhV monitoring program in Australia and provide an acceptable protocol to the OPR together with time frames regarding implementation and reporting of outcomes. If the sponsor does not plan to implement this programme in Australia, satisfactory justification should be provided.
- It was acceptable that the educational program with respect to the potential for medication errors with the 50 mL vial do not need to be implemented in Australia; however it is recommended that the sponsor introduce the component of the educational material (DCF) pertaining to the Revatio hypotension PhV monitoring programme as part of the risk minimisation activities for the hypotension risk..

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator recommended approval with respect to chemistry and quality control. The product is a simple IV injection and acceptable expiry and release limits were specified along with suitable limits for appearance, sterility, bacterial endotoxins, subvisible particles and extractable volume. The evaluator noted that the levels of sildenafil from a 10 mg IV injection will be approximately 12% lower than for the 20 mg tablet.

Nonclinical

The nonclinical evaluator had no objections to the registration of sildenafil for the proposed indication. No new nonclinical data were submitted, however previous studies were submitted using IV dosing that supported the efficacy of sildenafil. There was no evidence of local toxicity following repeated IV dosing in rats and rabbits at concentrations of sildenafil that were 3-6 times greater than clinically expected.

Clinical

Clinical Evaluation

The clinical evaluator recommended approval in the evaluation report for the proposed indication. The concerns noted by the evaluator included:

- Lack of data on the haemodynamic effects of bolus injection
- Limited safety data on the effects of a bolus injection

Pharmacology

Study A1481262

This was an open label single dose study of the safety, tolerability and pharmacokinetics of 10 mg IV bolus dose in 10 pulmonary arterial hypertension (PAH) patients who were stable on and tolerated 20 mg tds oral sildenafil. Eight of the ten patients were receiving bosentan which increases the clearance of sildenafil by 60%. The mean C_{max} was 240 ng/mL and the maximum C_{max} was 433 ng/mL which is within the range deemed to be safe from previous IV studies. Changes in blood pressure were around 10 mmHg at 30 minutes and 1 hour post dose. However there were no blood pressure assessments prior to 30 minutes which may underreport any effects but the evaluator did not see this as a major deficit. There were no episodes of hypotension or dizziness. The evaluator commented that the C_{max} was unlikely to be influenced by the presence or absence of bosentan.

Study A1481024

This was a randomised placebo controlled study in 45 PAH patients of IV sildenafil targeting predetermined plasma concentrations. This study was of less relevance as patients were given 20 minute infusions rather than the bolus dosing proposed in this submission. The study indicated that the selected infusion rates approximately achieved the targeted concentrations. A population pharmacokinetic analysis was conducted but this did not consider bolus dosing. Pulmonary vascular resistance data was limited but indicated a favouring towards the 100 ng/mL concentration.

Study A148-208

This was an absolute bioavailability study of 50 mg IV sildenafil vs 50 mg oral sildenafil in 12 healthy volunteers. The study indicated the absolute bioavailability of sildenafil from the oral tablet to be 41% and the C_{max} of the oral was 30% of the IV product. The T_{max} for the IV was half of the oral preparation (0.73 vs 1.46 hours). The data support the proposed dosing in the PI of 10 mg tds for the IV compared to 20 mg tds for the oral, given the absolute bioavailability of 41% is close to half for the oral (Table 3).

Study A148-203

This was an intravenous infusion study in 8 healthy volunteers comparing 3 doses of sildenafil (20, 40 or 80 mg) which showed an almost linearity in pharmacokinetic parameters and that concentrations beyond the proposed dose in the PI were well tolerated. However this study was not directly relevant as it was an infusion study. PK modelling of this study indicated that the C_{max} of a 10 mg bolus dose would be 203 ng/mL. This is close to the actual results from study A1481262 which showed it was a mean 240 ng/mL. Another PK model of this study with studies A148-208 and A148-211 (not submitted) indicated bosentan would increase the clearance of sildenafil and reduce AUC by 63% but not significantly affect the C_{max} , as expected.

Study A148-301

This pharmacodynamic study of sildenafil infusions in a different population (ischaemic heart disease) was not directly relevant but indicated that higher doses of sildenafil (for example, 20 mg and 40 mg) were well tolerated.

Efficacy

No new data were submitted.

Safety

Exposure was limited in this dataset with only one study using a bolus IV injection of sildenafil and the other using a slow infusion. In this main study of 10 PAH patients (Study

A1481262), two subjects had falls in systolic BP of >20 mmHg in the first hour post dose but were not symptomatic and two patients had flushing. In Study A1481024, 17 adverse events in 12 patients were considered treatment related with the most common being vasodilation, hypotension, headache and nausea and 3 events were considered severe (hot flush, headache and nausea). No laboratory abnormalities were considered treatment related. Adverse events reported in the other studies included headache, haemorrhage at injection site, vasodilation, dizziness, pulmonary hypertension, hypotension, back pain and penile erection. Adverse events in these other studies were mainly mild, dose related and there were no laboratory abnormalities that were treatment related. Postmarketing experience data was limited to infusions of sildenafil in small studies using doses greater than 10 mg.

Risk Management Plan

The Office of Product Review has accepted RMP, Version 4.6 for sildenafil. The sponsor committed to an additional risk minimisation strategy focusing on a hypotension monitoring program in Australia and will report on the outcomes annually. The program will include an educational pack for healthcare professionals.

Risk-Benefit Analysis

Delegate Considerations

Pharmacology

There was no new efficacy data submitted, therefore the evidence to support this presentation is based on pharmacology data. The exposure from a 10 mg IV injection is said to be similar to a 20 mg oral tablet, however the chemistry evaluator has noted this is in fact about 12% lower. The clinical evaluator has commented that the absolute bioavailability was about 41% from an oral tablet compared to IV administration which is close to the recommended halving of the dose when given by the IV route. These slight differences are unlikely to be clinically significant. The pharmacology studies support the tolerability of the 10 mg IV dose based on the higher doses used in other studies and that the C_{max} is unlikely to be affected by bosentan or CYP3A4 inhibitors. Accumulation is unlikely to occur and the proposed dose of 10 mg tds IV is expected to produce a similar plasma profile as the 20 mg tds oral dose. The clinical evaluator noted that the population in the main IV bolus study was slightly different to the currently accepted oral studies but still sufficiently similar to extrapolate data across.

Applicability to all indications

The indication proposed could be used for adults or children however the data submitted and proposed statements in the PI for dosage only relate to the adult population, therefore the indication should reflect the adult population. However it is uncommon for a new presentation to have a specific indication, therefore the sponsor could consider the option of removing the indication and simply containing the information in the Dosage section of the PI but with amendments to it being for the adult population.

Safety and RMP

The safety data are very limited for bolus dosing but there is some reassurance from the use of the oral tablet and higher doses of the IV infusion. The data that were available indicate acceptable tolerability even at doses beyond those proposed with headache and flushing being the most common adverse events. The safety profile from the IV injection appears to be similar to the oral tablet based on the limited data. The main concern is hypotension soon after dosing and the lack of blood pressure data within the first 30 minutes of dosing is also a significant deficit. However no significant episodes of

hypotension occurred. To address this concern, an acceptable RMP has been agreed with the sponsor including the implementation of a hypotension monitoring program for healthcare professionals.

List of Questions and sponsor response

The sponsor has responded to the clinical evaluator's list of questions. No new data on the pharmacodynamics of IV bolus dosing are anticipated and no data on the blood pressure effects of bolus dosing prior to 30 minutes are available. The sponsor noted that as of 1 June 2011, there has been limited use of IV sildenafil overseas and that so far 7 cases of hypotension have been reported.

Other data deficiencies

There were no efficacy data presented with IV sildenafil and limited pharmacology and safety data.

Summary

The evidence for IV bolus dosing relies on a single pharmacology study with supportive evidence from IV infusion and oral tablet studies. Although this is very limited information, the established efficacy and safety of the oral tablet, the seriousness of the disease and the placement of this treatment option as second line to oral therapy in patients who are already prescribed oral sildenafil and temporarily unable to take oral treatment and are clinically and haemodynamically stable is a reasonable approach. The main safety concern is with hypotension for which an RMP and monitoring program has been agreed. Overall the submission appears approvable for the proposed indication; however it was recommended that the EU wording be used instead.

The Delegate proposed to approve the submission for the following indication:

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 sponsor should address the following issue in the Pre-ACPM response:

- Please provide an update on reports of hypotension or other serious adverse events associated with intravenous sildenafil usage.

The Delegate also directed the following question to the ACPM:

- Is the limited pharmacokinetic data sufficient to support the registration of sildenafil solution for injection?

Response from Sponsor

The sponsor revised the Indication section of the PI as requested to that of below:

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 sponsor also responded to questions asked by the Delegate.

Serious Adverse Events (SAE)

In addition to the information relative to the 7 cases reporting the AE of hypotension (regardless of causality and seriousness) associated with the use of Revatio Solution for Injection and provided to the Delegate by the sponsor in the previous set of responses to the clinical evaluation report, safety information was available on 3 other cases that

reported other AEs. Case narratives were provided and it was noted that none of these 3 cases reported SAEs.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

In expressing its view that the submission was suitable to be considered for approval the ACPM agreed with the Delegate that the overall risk benefit profile was positive. The ACPM considered the following matters:

The ACPM noted that pulmonary artery hypertension (PAH), left untreated, has a grave prognosis. There is a risk that the abrupt cessation of sildenafil when used for the treatment of PAH in patients who temporarily cannot take oral medication may lead to a worsening of their condition. This is particularly a concern in patients who are undergoing major surgery where there is a risk of a pulmonary artery hypertensive crisis.

It was further noted that there were no new efficacy data submitted and therefore the evidence to support this presentation relied on pharmacology data.

With respect to chemistry, quality control and nonclinical issues there were no outstanding questions. In consideration of the slight bioavailability differences between oral tablet and IV infusion these were unlikely to be clinically significant.

Safety: The safety data are very limited for bolus dosing but there is some reassurance from the use of the oral tablet and higher doses of the IV infusion and the safety profiles of the oral and IV injection appear to be similar. The main concerns are hypotension soon after dosing and the lack of blood pressure data within the first 30 minutes of dosing. However, no significant episodes of hypotension occurred. Monitoring to address this concern is essential.

The committee agreed with the Delegate's view that in light of the lack of data provided on safety in children the new presentation should be limited to adults.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Revatio solution for injection vial containing sildenafil citrate 10 mg/12.5 mL and 40 mg/50 mL for the new indication:

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.

Included among the specific conditions of registration was the following:

- The implementation in Australia of the sildenafil Risk Management Plan (RMP), version 4.6, and the commitments made in the sponsor's Risk Management Plan Response dated 21 January 2011 and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

REVATIO[®]

(sildenafil citrate)

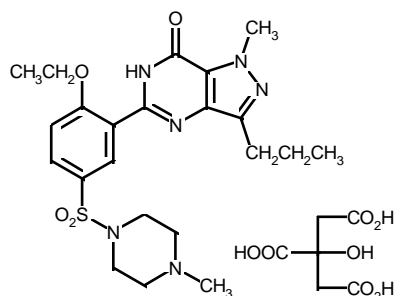
NAME OF THE MEDICINE

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 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. CAS number 171,599-83-0.

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

Sildenafil citrate has the following structural formula:-



DESCRIPTION

Sildenafil citrate is an off-white, crystalline powder with a molecular weight of 666.7. Its aqueous solubility is equivalent to 2.6 mg sildenafil per mL at 25°C.

In addition to sildenafil citrate, each REVATIO tablet contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, glycerol triacetate.

In addition to sildenafil citrate, REVATIO solution for injection contains glucose and water for injections. It is a clear, colourless solution.

PHARMACOLOGY

Pharmacological actions

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*.

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. PHARMACOKINETICS

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 (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 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 40% 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 h. 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.

Elimination

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

Renal impairment

In volunteers with mild ($\text{Clcr} = 50\text{-}80 \text{ mL/min}$) and moderate ($\text{Clcr} = 30\text{-}49 \text{ mL/min}$) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe ($\text{Clcr} = <30 \text{ mL/min}$) 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 (84%) 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.

Elderly (over 65 years of age)

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 %.

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 (t.d.s.), 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.

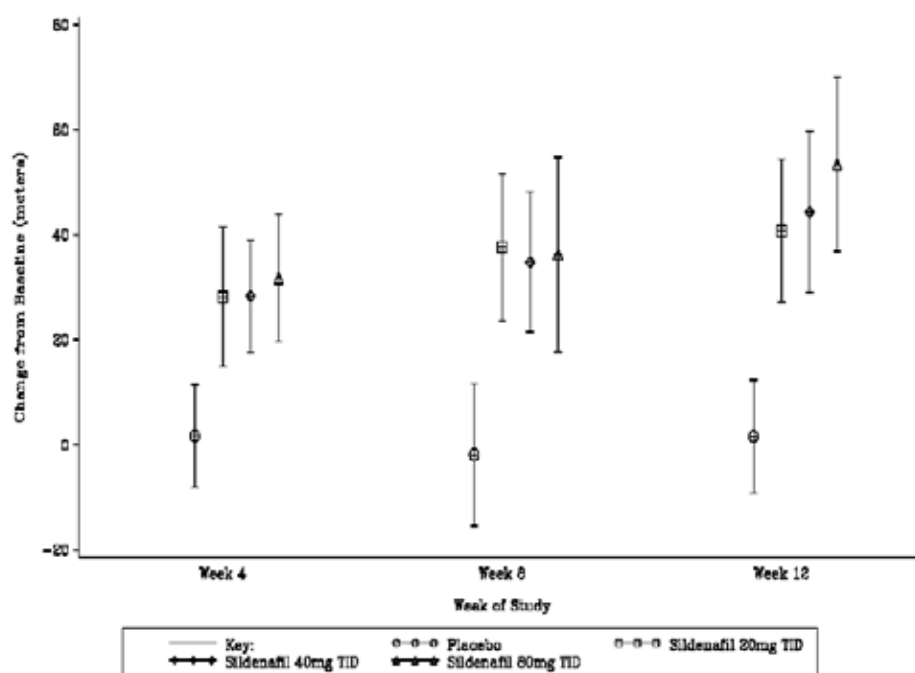
CLINICAL STUDIES

A randomized, double-blind, placebo-controlled study was conducted in 277 patients with pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure ≥ 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 randomized to receive placebo (n=70) or REVATIO 20 mg (n=69), 40 mg (n=67) or 80 mg (n=71) t.d.s. 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 of 378 meters and 326 meters respectively; fewer patients were Class I (1/277, 0.4%) or IV (9/277, 3%).

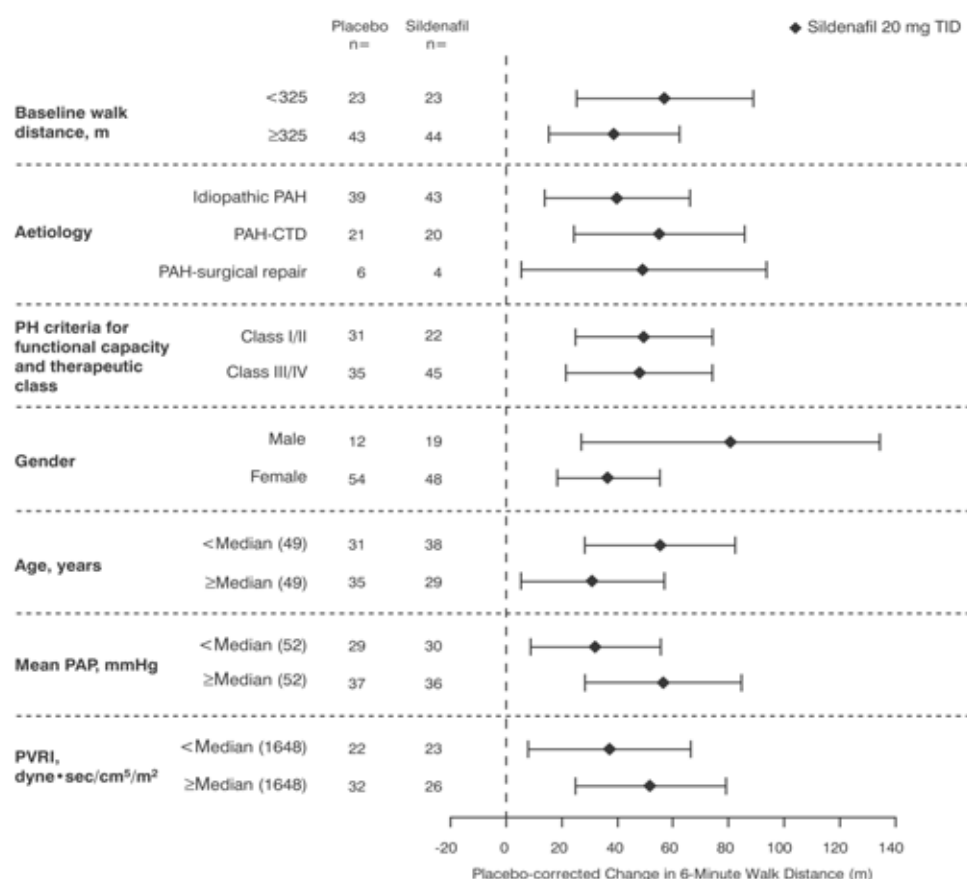
The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance. A statistically significant increase in 6-minute walk distance was observed in all 3 sildenafil dose groups compared to those on placebo. Placebo corrected increases in walk distance were 45 metres (p <0.0001), 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 CTD-associated PAH), WHO functional class, gender, race, location, mean PAP and PVRI (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 t.d.s. produced a placebo-corrected decrease in mPAP of -2.7 mmHg, -3.0 mmHg, and -5.1 mmHg, respectively. There was no evidence of a difference in effect between sildenafil 20 mg t.d.s. and the higher doses tested (See DOSAGE AND ADMINISTRATION). Data from other haemodynamic parameters can be found in Table 1. The relationship between these effects and improvements in 6-minute walk distance is unknown.

Table 1. Changes from Baseline to Week 12 in Haemodynamic Parameters at Sildenafil 20 mg t.d.s. Dose

PARAMETER [mean (95% CI)]	Placebo (N=65)*	Sildenafil 20 mg t.d.s (N=65)*
PVR (dyn·s/cm⁵)	49 (-54, 153)	-122 (-217, -27)
SVR (dyn·s/cm⁵)	-78 (-197, 41)	-167 (-307, -26)
RAP (mmHg)	0.3 (-0.9, 1.5)	-0.8 (-1.9, 0.3)
CO (L/min)	-0.1 (-0.4, 0.2)	0.4 (0.1, 0.7)
HR (beats/min)	-1.3 (-4.1, 1.4)	-3.7 (-5.9, -1.4)

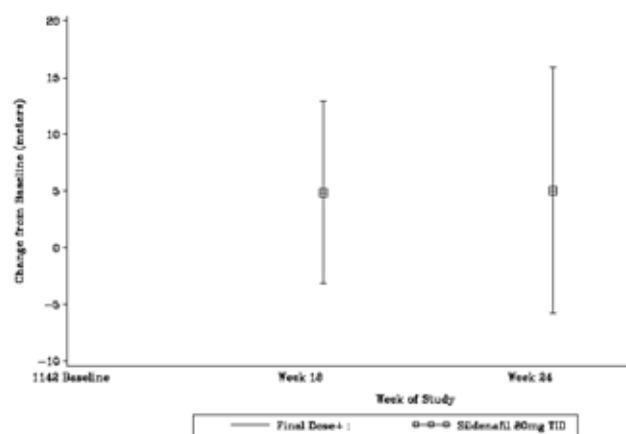
*The number of patients per treatment group varied slightly for each parameter due to missing assessments.

Extension Study

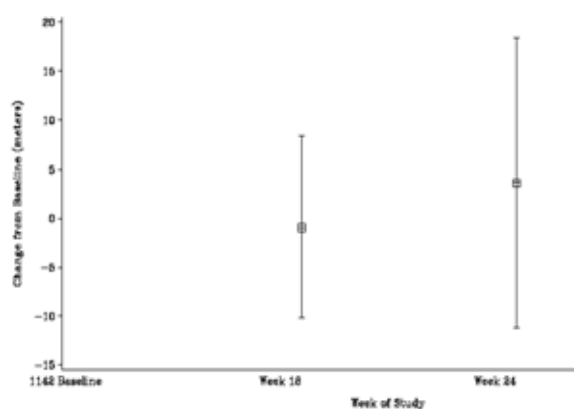
Following the pivotal study, 259 of the 277 REVATIO-treated patients entered an extension study, for which an interim data analysis was performed after 24 weeks of therapy. In the extension study, patients were allocated to either one of two dosage regimens (A or B). In regimen A patients received 40 mg sildenafil for 6 weeks and were then titrated to 80 mg for the remainder of the study. In regimen B, patients received 80 mg sildenafil for 6 weeks and were then dummy titrated to 80 mg. Patients who had initially been on 20 mg or 40 mg were allocated to regimen A while those initially on 80 mg were allocated to continue 80 mg in Regimen B. Patients could be down-titrated if they did not tolerate the 40 mg or 80 mg 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 (A), sildenafil 40 mg (B), and sildenafil 80 mg (C)

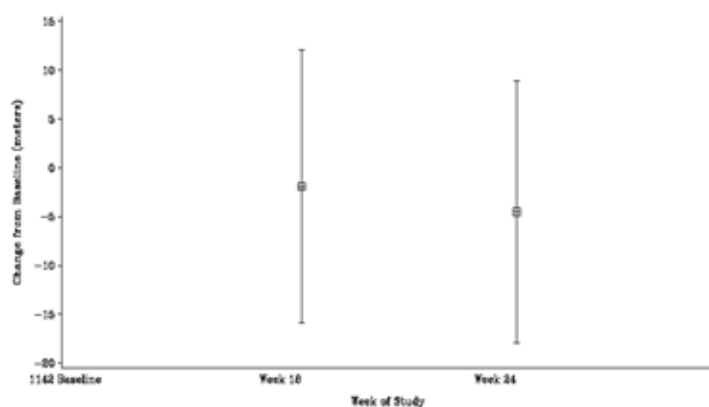
(A)



(B)



(C)



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

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 minute post dose. The mean changes from baseline in sitting blood pressure were greatest at 1 hour, -9.1 mmHg (SD \pm 12.5) and -3.0 (SD \pm 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.

INDICATIONS

Oral REVATIO is 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 evaluated in patients currently on bosentan therapy.

CONTRAINDICATIONS

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

Nitrates and sildenafil 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).

REVATIO is not recommended in patients with pulmonary arterial hypertension with a previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (see PRECAUTIONS, ADVERSE EFFECTS - Post Marketing Data, 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).

PRECAUTIONS

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 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 mmHg), 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. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see CONTRAINDICATIONS and ADVERSE EFFECTS – Post Marketing Data-Other Events).

Anatomical deformation of the penis or predisposition to 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).

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 INTERACTIONS WITH OTHER MEDICINES). 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.

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 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.

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.

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 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/m² 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

No information is available on its secretion into breast milk. Sildenafil should not be administered to breast-feeding mothers.

Paediatric Use

Safety and effectiveness in paediatric pulmonary hypertension patients has not been established.

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.

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.

INTERACTIONS WITH OTHER MEDICINES

Effects 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. 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 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.

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 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 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 specific CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), there was a 182 % increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max} , T_{max} , elimination rate constant, or subsequent half-life of sildenafil or its 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 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.

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

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

Co-administration of oral contraceptives (ethinylloestradiol 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.

Effects 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 (IC₅₀ >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 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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).

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 CONTRAINDICATIONS).

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

ADVERSE 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. 259 subjects who completed the pivotal study entered a long-term extension study. Doses up to 80 mg t.d.s. (4 times the recommended dose of 20 mg t.d.s.) 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 t.d.s. 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 t.d.s. doses, and more commonly on REVATIO than on placebo, are shown in Table 2.

Table 2. Sildenafil Adverse Events More Frequent than Placebo in $\geq 3\%$ 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 $\geq 1\%$ 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, cellulitis.

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 Data

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. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (See CONTRAINDICATIONS and PRECAUTIONS).

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 PRECAUTIONS).

Other events, reported post marketing at 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

Eye disorders: eye pain, red eyes/bloodshot eyes

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

DOSAGE AND 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 three times a day (tds). 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 tds therefore treatment with doses higher than 20 mg tds is not recommended (See CLINICAL TRIALS). Dosages lower than 20 mg tds 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 the Elderly (over 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 PHARMACOKINETICS, Elderly).

Use in Patients with Impaired Renal Function

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 PHARMACOKINETICS, Renal Impairment regarding increased exposure in patients with severe renal impairment).

Use in Patients with Impaired Hepatic Function

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 PHARMACOKINETICS, Hepatic Impairment)

Use in Children (< 18 Years)

Safety and effectiveness in paediatric pulmonary hypertension patients has not been established. Therefore sildenafil is not recommended for use in these patients.

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.

Use in Patients using other PAH Medicines

The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg. bosentan, epoprostenol, iloprost) has not been studied in controlled clinical trials. Therefore the concomitant use of sildenafil with these medicinal products cannot be recommended (see PRECAUTIONS – Interaction with Other Medicines).

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 CONTRAINDICATIONS and PRECAUTIONS - INTERACTIONS WITH OTHER MEDICINES for dosing instructions.

Refer also to the PHARMACOKINETICS section for information regarding the pharmacokinetics of the intravenous formulation.

OVERDOSAGE

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.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

REVATIO tablets contain 20 mg sildenafil (as the citrate). Tablets are white, round film-coated marked “Pfizer” on one side and “RVT 20” on the other and supplied in PVC blister packs of 90 tablets.

REVATIO solution for injection is a clear, colourless solution supplied as 12.5 mL and 50 mL⁺ in a clear, type I glass vial with a chlorobutyl rubber stopper and an aluminium overseal.

⁺ The 50 mL vial presentation is not commercially available.

Shelf life

Oral: 5 years when stored below 30°C.

Solution for injection: 3 years when stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF APPROVAL:

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