



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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- 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 and Major Variation
<i>Decision:</i>	Withdrawn
<i>Date of Decision:</i>	11 August 2011
<i>Active ingredient(s):</i>	Sildenafil citrate
<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>	Tablet, oral suspension
<i>Strength(s):</i>	10 mg/mL oral suspension compounded from a 20 mg tablet
<i>Container(s):</i>	Amber glass or HDPE bottle
<i>Pack size(s):</i>	124 mL
<i>Approved Therapeutic use:</i>	There was no change to the currently approved indication: Revatio is used to treat 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. The efficacy of Revatio has not been evaluated in patients currently on bosentan therapy.
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	There was no change to the current dosage of 20 mg three times daily
<i>ARTG Number:</i>	119102

Product Background

Revatio (sildenafil) is used to treat patients with pulmonary arterial hypertension (PAH) 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. The efficacy of Revatio has not been evaluated in patients currently on bosentan therapy.

This AusPAR describes the evaluation of an application by Pfizer Australia Pty Ltd (the sponsor) to extend the indications of Revatio (sildenafil citrate) 20 mg film coated tablets to include the treatment of paediatric patients aged 1 to 17 years with PAH.

Pulmonary hypertension is a rare, progressive and life threatening disease with the incidence of PAH in children the same as in adults (1 -2 per million in Western countries). There are a number of treatments available for PAH in adults including PDE5 inhibitors

such as sildenafil, endothelin receptor antagonists and prostanoids. According to the sponsor, these agents have been approved following the conduct of randomised controlled trials usually of 12 to 16 weeks duration, using exercise capacity as an endpoint. To date, there have been no large randomised controlled trials in children with PAH and therefore there are few data available on the safety and efficacy of these agents in the paediatric population. This is despite the fact that paediatric PAH is a severe disease and disease progression appears more rapid than in adults.

There are currently no approved treatments for PAH in children. Revatio offers a potential treatment for this severe and progressive disorder in children aged 1 -17 years. Unlike adults, children are unable to consistently perform the 6 minute walk test (6-MWT). In consultation with the EU regulatory agency, the sponsor has used the partial pressure of oxygen in venous blood (pVO₂) as measures by a graded test on an exercise bike as the primary outcome measure of efficacy in this age group. The ultimate aim is improved long term survival and quality of life. Such data will not be available for many years and so short term surrogate markers as proposed in the submission are appropriate.

The proposed extension of indication is as follows:

Treatment of paediatric patients aged 1-17 with pulmonary arterial hypertension. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

The submission also proposed to amend the product information (PI) to allow the currently registered 20 mg sildenafil tablet (Revatio) to be prepared extemporaneously by pharmacists into an oral suspension. This oral suspension would be used by paediatric patients with pulmonary arterial hypertension who are unable to swallow the tablet or require a dose of less than 20 mg.

Regulatory Status

An identical application was submitted to the European Union (EU) on 10 February 2010. The application was approved on 2 May 2011 with the following indication:

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

II. Quality Findings

Drug Substance (active ingredient)

There was no change to the previously approved drug substance.

Drug Product

Formulation and manufacture

In patients who are unable to swallow the tablet or require a dose of less than 20 mg an extemporaneous preparation is prepared by crushing registered tablets and compounding with two ingredients (Ora-Sweet and Ora-Plus). This is to be performed by a pharmacist. There were initial questions relating to availability of, and the quality of the excipients in Ora-Sweet and Ora-Plus. However, data were provided to demonstrate that the proposed compounding mixtures (Ora-Sweet and Ora-Plus) are of suitable quality.

There were also data which indicated that the resulting suspension will remain sterile over the storage period (that is, 30 days; see *Stability*) and a suitably accurate device will be used to dispense the suspension.

It was noted that 62 x 20 mg sildenafil tablets will be used to prepare the oral suspension which is incongruous with the current pack size of 90 tablets.

Stability

Stability data were provided to demonstrate that the resulting suspension is chemically and physically stable when stored at 2-8°C for at least 30 days (the maximum time proposed) in natural high density polyethylene (HDPE) bottles with white polypropylene caps. The resulting suspension has the additional storage condition 'do not freeze'.

Bioavailability

The clinical efficacy studies used either the registered 20 mg Revatio tablet or this tablet crushed and given with apple sauce. The sponsor provided a bioavailability study which compared these two treatments with the proposed oral suspension. Bioequivalence was demonstrated but the rate of response (maximum plasma concentration, C_{max}) was lower.

Advisory Committee Considerations

Details of this submission were presented at the 136st meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in January 2011. The PSC:

- Noted the paucity of bioequivalence data (*the lack of method validation and individual results*).
- Considered that the sponsor should be asked to provide the results of microbiological testing at the end of a study simulating the proposed in use scenario.
- Considered that the sponsor should be asked to justify the rationale of using 62 x 20 mg tablets given that a similar suspension could be compounded by using 12 x 100 sildenafil tablets.

The first of these issues was resolved to the satisfaction of the TGA and the PSC did not request to review this submission again. In relation to the last issue, the arguments of the sponsor were provided to the Delegate for consideration.

Quality Summary and Conclusions

Approval of the changes to chemistry and quality control aspects of the product information (PI) were recommended. The following were brought to the attention of the Clinical Delegate for consideration:

- Whether the use of 62 x 20 mg sildenafil tablets to prepare the oral suspension is acceptable when the tablets are only supplied in packs of 90; and the suspension could equally be prepared from 12 x 100 mg sildenafil tablets.
- If the noted drop in C_{max} is clinically relevant

III. Nonclinical Findings

Introduction

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

No nonclinical studies involving dosing of juvenile animals were submitted. As justification, the sponsor stated that as there were no new safety signals arising from clinical trials with paediatric patients, no additional nonclinical studies were conducted. Further discussion of the lack of studies in juvenile animals, based on points to consider in the relevant TGA-adopted EU guidance may have been beneficial.¹ This issue is discussed further below. Thus, the evaluation of the nonclinical safety of sildenafil for use in children will rely on existing nonclinical data, namely the original registration application for sildenafil tablets and for the PAH indication in adult patients.

The sponsor proposed an oral liquid formulation (extemporaneously prepared suspension) for patients who are unable to swallow the tablet or require a dose of less than 20 mg, comprising crushed tablets in a 75:25 mixture of Ora-Sweet and Ora-Plus. This issue is discussed further under *Safety of liquid formulation* 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 intravenous (IV) dosing of sildenafil ($\geq 1.5 \mu\text{g}/\text{kg}$), with resulting free plasma sildenafil concentrations of $\geq 5 \text{ nM}$ ($3.3 \text{ ng}/\text{mL}$; about 14 times lower than the clinical C_{max}).² There is no evidence to suggest that this effect will not occur in paediatric patients. Thus, the available nonclinical efficacy data are supportive for efficacy of sildenafil in paediatric patients.

Pharmacokinetics

Metabolism of sildenafil in humans is mediated by cytochrome P450 (CYP) 3A4 and CYP2C9 (according to the sponsor's *Nonclinical Overview*, the former appears to be more important at clinical doses). Maturation of CYP3A4 expression occurs primarily during the first year of life; expression of CYP3A4 at one year is estimated to be 72% of expression in adults.³ The fetal form of this enzyme, CYP3A7, is present at high levels at birth and its activity declines in conjunction with increases in CYP3A4 activity.⁴ An *in vitro* study submitted with a concurrent application for a new dosage form of sildenafil demonstrated that clearance of sildenafil by recombinant human CYP3A7 was around 25-fold lower than that of CYP3A4. Thus, exposure to sildenafil may theoretically be greater in children of around one year of age, resulting in a greater potential for adverse effects. This issue should be addressable by clinical data; the potential need for adjustment of dosage levels in very young patients was referred to the clinical evaluator/Delegate.

The available nonclinical pharmacokinetic data do not indicate any other potential concerns in paediatric populations compared with adults.

Relative exposure

Pharmacokinetic data were reported for paediatric PAH patients in one clinical trial with oral sildenafil; respective predicted AUC based exposure following administration of the recommended dose to patients in the two indicated body weight groups for 16 weeks was 371 ng.h/mL (10 mg tds for patients $< 20 \text{ kg}$) and 486 ng.h/mL (20 mg tds for patients

¹ EMEA, Committee for Medicinal Products for Human Use (CHMP), 29 September 2005. Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005).

² Refer to 'Relative exposure' below for a discussion of clinical C_{max} values.

³ Johnson TN *et al.* Development of CYP2D6 and CYP3A4 in the first year of life. *Clin Pharmacol Ther* 2008; 83: 670-671.

⁴ Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. Part II. *Clin Pharmacokin* 2002; 41: 1077-1094.

≥ 20 kg); respective predicted C_{\max} values were 112.8 ng/mL and 107.6 ng/mL. For reference, AUC based exposure in a clinical trial in adult males at 25 mg tds orally, was 361 ng.h/mL and the clinical C_{\max} was 127 ng/mL. Assuming linear pharmacokinetics, extrapolated exposure levels at the recommended dosage level for treatment of PAH in adults (20 mg tds) were 289 ng.h/mL (AUC) and 102 ng/mL (C_{\max}). As AUC based exposure with both paediatric dosing regimens was greater than that calculated in adults, re-calculation of relative exposure levels in nonclinical studies compared with paediatric exposure levels is required. A re-assessment of C_{\max} based relative exposure was not considered necessary, as the potential for acute effects (C_{\max} related) in paediatric patients should be adequately addressed in previous assessments of sildenafil, based on similar C_{\max} values in paediatric patients compared with adults.

The pharmacokinetic data reported for both adults and children were predicted by pharmacokinetic pharmacodynamic (PK-PD) modelling of sparse data points in a large number of patients, rather than direct calculation following determination of sildenafil plasma concentration time profiles. This approach may be limited by many factors, such as inter-individual variability, extent of existing knowledge, complexity of the data analysis techniques, potential for introduction of bias and study design (for example, timing of sampling in relation to actual C_{\max} and the minimum plasma concentration [C_{\min}]).^{5,6} Therefore, the predicted paediatric pharmacokinetic parameters are considered to be relatively broad estimates only.

Toxicokinetic data from previously evaluated repeat dose toxicity studies are reproduced below for ease of reference; data from the long term studies in rats and dogs were considered to be most representative and were used in this report for calculating relative exposure compared with paediatric patients. However, blood sampling was relatively limited in these studies (4–5 time points in 24 hours [h]), leading to some uncertainty regarding the accuracy of nonclinical pharmacokinetic parameters. Thus, together with the described limitations associated with clinical PK-PD modelling, any exposure margins in nonclinical studies must be interpreted with caution.

Exposure levels (plasma AUC based) of sildenafil from these studies were compared with the maximum exposure calculated for a proposed clinical paediatric dosing regimen. The proposed paediatric dose of sildenafil is 10 mg tds for patients >20 kg (≥ 1.5 mg/kg/day), and 20 mg tds for patients ≥ 20 kg (≤ 3 mg/kg/day). As seen above, predicted sildenafil exposure was greatest with the maximum recommended paediatric dosing regimen and an AUC value of 486 ng.h/mL was used for relative exposure comparisons. Based on the similarity of sampling times used to calculate AUC values in different species ($t=6-8$ h in rats and dogs, and 8 h in humans), a direct comparison of AUC values was considered appropriate. Results are summarised in Table 1. Pharmacokinetic data for an active metabolite of sildenafil (N-demethylated sildenafil) were also obtained in nonclinical studies; exposure comparisons for this metabolite at the maximum recommended clinical dose are also included in the table. 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 the No Observable Adverse Effect Levels (NOAELs) for respective studies.

⁵ Lavé T et al. Challenges and opportunities with modelling and simulation in drug discovery and drug development. *Xenobiotica* 2007; 37: 1295-1310.

⁶ Jackson KA, Rosenbaum SE. The application of population pharmacokinetics to the drug development process. *Drug Dev Ind Pharm* 1998; 24: 1155-1162.

Table 1: Relative exposure (AUC) in long-term oral repeat dose toxicity studies

Study details	Sex	Dose (mg/kg/day)	Analyte	AUC _{0-t} (ng.h/mL) ^a		Exposure multiple (AUC)	
				Total	Free ^b	Total	Free
Rat 6 months	M	[3]	Sildenafil	[NC]	[NA]	[NA]	[NA]
		12		NC	NA	NA	NA
		60		400	20	0.8	1.0
		[3]	NDM-sildenafil	[100]	[11]	[0.4]	[1.0]
		12		1700	187	8	17
		60		12000	1320	54	120
	F	[3]	Sildenafil	[700]	[35]	[1.4]	[1.8]
		12		5000	250	10	13
		60		31000	1550	64	82
		[3]	NDM-sildenafil	[300]	[33]	[1.3]	[3]
		12		2000	220	9	20
		60		60000	6600	268	600
Dog 12 months	M/F	[3]	Sildenafil	[1100]	[154]	[2.3]	[8]
		10		4970	696	10	37
		50		32450	4543	67	239
		[3]	NDM-sildenafil	[220]	[31]	[1.0]	[2.8]
		10		1010	141	5	13
		50		4960	694	22	63
Paed. Patients ^c	M/F	20 mg tid	Sildenafil	486	19	NA	NA
			NDM-sildenafil	224	11	NA	NA

^a t = 6–8 h, depending on the species

^b Calculated based on respective unbound sildenafil and N-demethylated sildenafil fractions of 0.05 and 0.11 (rats), 0.14 and 0.14 (dog) and 0.04 and 0.05 (human)

^c PAH patients aged 1–17 yrs; ≥20 kg

NA = not applicable; NC = not calculated; NDM-sildenafil = N-demethylated sildenafil

NOAELs are shown in [brackets]

Toxicology (Safety)

No nonclinical safety studies conducted in juvenile animals were submitted. According to the TGA-adopted EU guidance, several nonclinical and clinical aspects must be considered when assessing the need for juvenile animal studies.¹ As discussed in previous evaluation reports for sildenafil, the primary target organs/tissues of toxicity in nonclinical studies with sildenafil are consistent with its primary pharmacology and include the cardiovascular system (vascular smooth muscle), the retina, platelets and gastrointestinal smooth muscle. As these target tissues are considered to be essentially developmentally equivalent to adults in the indicated paediatric population, no additional concerns are predicted to arise due to effects on developmentally immature target organs.

Although the mechanism of action of sildenafil and the identified target organs do not indicate any potential for new or exacerbated toxicity in paediatric patients, the young age of the intended population (≥1 years) and anticipated chronic administration are of concern. The theoretical potential for increased adverse events due to increased exposure

to sildenafil in patients around one year of age is discussed under *Pharmacokinetics* above. Exposure (AUC) to sildenafil and its active metabolite in nonclinical studies at NOAELs was generally similar to or greater than exposure in paediatric patients at the maximum recommended dose, except for male rats, which showed species specific sex differences in pharmacokinetics. Although the relative exposure margins were generally adequate, nonclinical studies in juvenile animals may have provided some additional reassurance about the safety of sildenafil for paediatric patients. In the absence of this supporting data, the safety assessment of sildenafil will rely primarily on clinical data.

Histopathology of the eye

Four new study reports were submitted, comprising ocular histopathology analysis of rats and dogs in long term oral (PO) repeat dose toxicity studies with sildenafil. The relevant toxicity studies have been evaluated previously, while the eye histopathology reports do not appear to have been evaluated by the TGA. There was no evidence for a treatment related effect on the retina, choroid or associated blood vessels in either species, in studies of up to 24 months duration in rats and 12 months in dogs.

Safety of liquid formulation

The sponsor proposes an oral liquid formulation (extemporaneously prepared suspension) for patients who are unable to swallow the tablet or require a dose of less than 20 mg, comprising crushed tablets in a 75:25 mixture of Ora-Sweet and Ora-Plus. However, these products are not listed or registered on the Australian Register of Therapeutic Goods (ARTG). The sponsor submitted a discussion of the availability of these two products in Australia and a risk assessment of the excipients present in Ora-Sweet or Ora-Plus.

The sponsor was reportedly advised by three major paediatric hospitals in Sydney that Ora-Sweet and Ora-Plus were commonly used when compounding paediatric formulations, including for compounding of sildenafil (sildenafil is Pharmaceutical Benefits Scheme [PBS] listed for paediatric use). According to the sponsor, the use of this formulation is intended only as an interim solution, pending the finalisation of development of a sildenafil powder for oral suspension.

The sponsor did not have access to the quantitative composition of Ora-Sweet and Ora-Plus, which are manufactured by Paddock Laboratories. Thus, the risk assessments are limited in most cases to a general, qualitative discussion of the safety of the presence of each excipient.

Glycerol (glycerin)

The sponsor estimated the maximum daily dose of glycerol in Ora-Sweet, based on the average density of the formulation and the volume administered, to be 5.45 g. This was less than limit of 10 g/dose proposed by the European Medicines Authority (EMA); thus, the presence of glycerol was considered acceptable.

Sorbitol

The sponsor used the same calculations for estimating the maximum dose of sorbitol in Ora-Sweet as for glycerol (maximum estimated daily dose = 5.45 g). As the same recommended limits (10 g/dose) apply for sorbitol, its presence was considered acceptable.

Sucrose

As a common component of food, the inclusion of sucrose in Ora-Sweet was considered acceptable. This formulation is not indicated for patients with hereditary sucrose intolerance, as reflected by PI statements.

Carrageenan

The safety of carrageenan was discussed by the sponsor in terms of recommendations by the joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2007, in which the acceptable dietary intake (ADI) for carrageenan as a food additive in foods other than infant formula was set as 'not specified'.⁷ This was defined as 'a term applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of the JECFA, represent a hazard to health'. In Australia, the only specified limits for carrageenan as a food additive in the Food Standards Code apply to products intended for consumption by infants.⁸ As the liquid formulation of sildenafil is indicated for patients ≥ 1 year of age, its inclusion in Ora-Plus is acceptable.

Methyl hydroxybenzoate (Methyl paraben)

The sponsor quoted opinion from the European Commission Scientific Committee on Consumer Products (2006 and 2008), stating that 'methyl paraben and ethyl paraben are not subject of concern'. This was considered acceptable, as methyl hydroxybenzoate is present in other ARTG listed or registered products.

Simethicone

The sponsor stated that simethicone is an active ingredient in some ARTG listed products intended for use by paediatric patients and that it is not absorbed from the gastrointestinal tract. Thus, its inclusion in Ora-Plus is considered acceptable.

Other excipients

The sponsor stated that the other excipients (microcrystalline cellulose, sodium carmellose, sodium phosphate, citric acid and potassium sorbate) are all listed as "Generally Recognised as Safe" by the FDA. All are contained in other ARTG listed or registered oral products, although it is unknown whether levels are comparable. The inclusion of these excipients is considered acceptable.

Based on the available data, the use of Ora-Sweet and Ora-Plus in a liquid formulation appears to be acceptable from a nonclinical perspective.

Nonclinical Summary and Conclusions

No nonclinical studies involving dosing of juvenile animals were submitted. Given the young age of the intended population (≥ 1 years) and anticipated chronic administration of sildenafil, such studies may have provided some additional reassurance about the safety of sildenafil for paediatric patients. The available nonclinical data do not indicate any potential for new or exacerbated toxicity in paediatric patients; however, in the absence of juvenile animal studies, the safety assessment of sildenafil will rely primarily on clinical data.

Previous *in vivo* primary pharmacodynamic data for sildenafil are indicative of efficacy in paediatric patients at clinically relevant doses.

Exposure to sildenafil may theoretically be greater in children around one year of age, due to immature CYP3A4 activity and lower clearance of sildenafil by the fetal form, CYP3A7 (shown to be around 25-fold lower than CYP3A4 *in vitro*). The potential for increased adverse effects in very young patients should be addressable by clinical data and the

⁷ FAO = Food and Agriculture Organization of the United Nations; WHO = World Health Organization

⁸ www.foodstandards.gov.au

potential need for adjustment of dosage levels in very young patients was referred to the clinical evaluator/Delegate.

Ocular histopathology analysis of rats and dogs from previous oral repeat dose toxicity studies (up to 24 months and 12 months duration, respectively) did not demonstrate evidence for a treatment related effect on the retina, choroid or associated blood vessels in either species.

There were no nonclinical objections to the change in patient population for sildenafil to include paediatric patients, provided the clinical data adequately demonstrate the safety of sildenafil in this group, particularly patients around one year of age.

There were no nonclinical objections to the proposed use of non ARTG listed/registered products (Ora-Sweet and Ora-Plus) in an oral liquid formulation of sildenafil.

IV. Clinical Findings

Introduction

The sponsor developed this submission in consultation with the European Regulator (EMA). The EU guidelines for the investigation of PAH are primarily aimed at the investigation of PAH in adults. This was discussed in the submission. The main deviation from the guidelines was the failure to include the 6 minute walk test (6-MWT) as the primary endpoint to measure improvement in exercise capacity. The sponsor argued that the use of the 6-MWT was inappropriate in a paediatric population and substituted the partial pressure of oxygen in venous blood (pVO₂) as the primary outcome measure. As part of the development process, the sponsor submitted a paediatric investigational plan (PIP) in compliance with the EU regulations. This plan must address the EMEA regulations and notes related to the development of paediatric medicines and the guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. As far as could be ascertained by the evaluator, the studies in the submission have complied with the PIP and the submission is stated to be the same as that submitted to the EMA. That the studies did comply with all of the requirements of the PIP should be confirmed by the sponsor.

Included in the submission were one pharmacodynamic study addressing taste and two pharmacokinetic studies. The efficacy and safety studies included one pivotal efficacy study with a continuing follow up longer term study of those patients who were continuing therapy from the pivotal study.

Pharmacodynamics

One taste study was submitted by the sponsor to investigate the most suitable extemporaneous liquid formulation for administration to children.

Study A1481257

This study was a single blind study in healthy adult volunteers to investigate the palatability of different oral suspension formulations of Revatio.

The study was conducted by a company with experience in assessing the palatability of pharmaceutical products. A team of four trained taste panelists were chosen who had passed tests evaluating their abilities to identify basic tastes, rank intensities and identify common odorants. Each subject had a screening visit within 28 days of administration of the Revatio formulations. On each study day, subjects assessed the palatability of the formulations using the Flavour Profile which assessed aroma, flavour, texture and mouth feel. Subjects received no more than four formulations in any one day and no more than

two formulations within a one hour period. All formulations were expectorated and not swallowed. The study found that the most palatable formulation was crushed Revatio tablets suspended in a 75/25 blend of Ora-Sweet/Ora-Plus at 10 mg sildenafil citrate/mL. The submission also commented that study drug formulations were judged to be of lower flavour quality.

Summary

The sponsor submitted one study which supports their extemporaneous formulation. This study supports the proposed extemporaneous formulation as the best tasting of those tested.

Pharmacokinetics

Two pharmacokinetic (PK) studies were included in the submission in support of the application. One (Study A1481275) was a bioequivalence study in support of the proposed extemporaneous preparation which is briefly summarised in *Section II*. In summary the study supports the bioequivalence of the EP formulation in the proposed PI with the crushed tablet formulation used in the pivotal study.

The other was a population pharmacokinetic analysis of the pivotal clinical study in children (Study 1481131).

Study A1481131

Study 1481131 was the pivotal clinical study of Revatio in the submission. The sponsor provided a population PK analysis based upon study 1481131. The stated objectives of the study included:

- Investigate the PK of sildenafil with PAH
- To develop a population PK model
- To identify influential covariates on the PK profile
- To estimate the ratio of exposure of metabolite/parent drug ratio
- To predict the range of mean steady state concentrations
- To develop a PD model of pVO₂

This study utilized a technique known as population pharmacokinetic approach to the analysis sparse data (that is each patient only supplied a few data points) using a complex computer algorithm known as non-linear mixed effects modelling (NONMEM). NONMEM is the gold standard program for performing these analyses. The study included pharmacodynamic (PD) data and the effect concentrations predicted included the concentration for 50% maximal effect (EC₅₀) and 90% maximal effect (EC₉₀) was predicted. The resulting equations are used to give PK and PD parameters and their variances which can be interpreted in much the same way as they are from a standard analysis.

The study took sparse pharmacokinetic data obtained during the 16 weeks from 173 patients in study 1481131. Dosing covered the range of 10 mg to 80 mg orally tds. The PK aimed to quantify the effect of age and/or body weight on clearance (CL/F). The population PK analysis combined data from both adult (Study A1481140) and paediatric (Study A1481131) patients in order to develop a model which describes the relationship between age/weight and pharmacokinetic parameters such as CL/F and apparent distribution volume (V/F). The PD analysis was based upon the paediatric PK. NONMEM version 6 was used for the analysis.

PK Analysis

A one compartment model with first order absorption (NONMEM/ADVAN2) was fit to the parent drug and metabolite concentrations. The dependency of CL/F with body weight increase was expressed by a sigmoid model with an intercept for parent drug concentration. F (bioavailability) includes a power model with dose. The adult study (Study A1481140) was not included in this submission but has been previously assessed by the TGA.

PD Analysis

pVO₂ values at baseline and Week 16 were included in the PK/PD modeling. Estimates of individual exposure, as predictors for the response, were derived from the population PK model using either the individual EBEs (Bayesian Estimates) of clearance or the TV (Typical Values) based on the covariates (dose and weight) only.

Results

PK Analysis

The one compartment model with first order absorption described the data. The PK model incorporated weight as the only covariate.

The estimated PK parameters are shown in Table 2 and a sigmoidal relationship between weight and clearance was determined. This demonstrates the modelled clearance plateaus at a body weight somewhere between 20 and 30 kg.

Table 2: Estimated PK parameters

Parameters	unit	Pointest	Covstep		95% CI	
			RSE %	SE		
TVKa	1/h	4.37	18.4	0.806	2.79	5.95
TVCL0	L/h	13.9	14.2	1.98	10.02	17.78
TVV	L	302	4.74	14.3	273.97	330.03
TVALAG1	h	0.241	1.59	0.00382	0.23	0.25
TVCLmax	L/h	57.8	4.62	2.67	52.57	63.03
WT50	kg	21.3	8.26	1.76	17.85	24.75
WT on V/F		0.655	11.8	0.0774	0.50	0.81
DOSEEXP		-0.221	24.7	0.0545	-0.33	-0.11
Gamma		3.7	23.5	0.87	1.99	5.41
MIX.ERR	ng/mL	1.8	13.8	0.249	1.31	2.29
H3A4 on CL/F		-0.323	13.9	0.0448	-0.41	-0.24
BETAB on CL/F		-0.343	20.2	0.0694	-0.48	-0.21
CV.KA		1.18	16.8	0.198	0.79	1.57
CV.CL		0.495	5.1	0.0253	0.45	0.54
CV.V		0.56	7.37	0.0413	0.48	0.64
Res		0.265	4.94	0.0131	0.24	0.29

The above TV for CL/F and V/F are these at BW = 53.1 kg and dose = 29.6 mg

PD Analysis

A sigmoid E_{max} model was successfully applied to the pVO₂ data. Two final models produced similar parameter estimates except for EC₅₀. The estimated parameters, based upon one of these models (the TV model), is shown in Table 3.

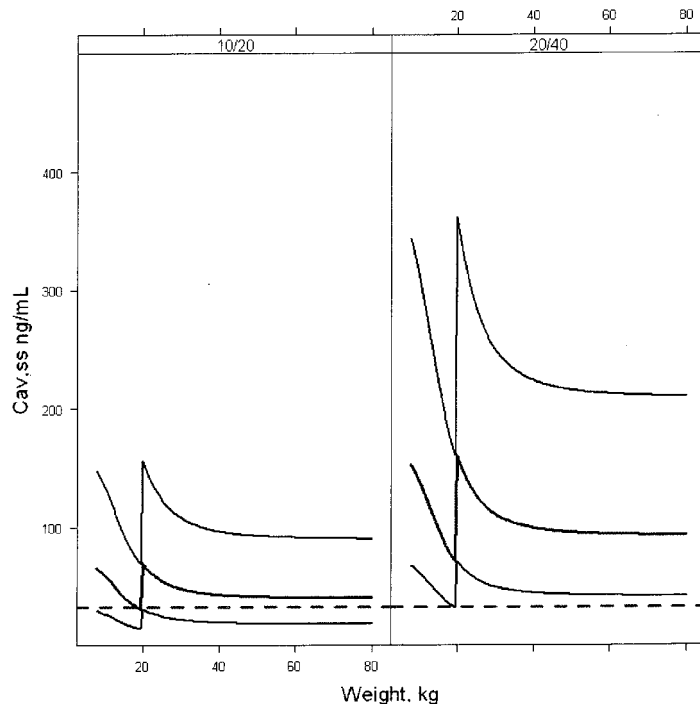
Table 3: Pop PK/PD estimates (TV model)

	MEAN	SEM	CV(%)	SD(%)	95% CI	
Baseline, pVO2	17.6	0.417	2.369	23.6	16.78	18.42
E _{max} , %	9.09	2.21	24.31		4.758	13.42
EC ₅₀ , ng/mL	23.7	3.59	15.15		16.66	30.74
Hill	8					
res-err, %	11.9					
EC ₉₀	31.19	4.727	15.16		21.93	40.46

Proposed Dosing Strategy

Based upon the PK-PD modeling, the sponsor suggested a dose cut-off at a body weight of 20 kg and supports the 10/20 dosing strategy proposed in the PI. The modeling is summarised in Figure 1. The centre plot lines show the mean drug concentration for each of the two dosing strategies; the upper and lower lines are the 90% confidence intervals (CI). The dashed horizontal line represents the EC₉₀ which was estimated at 32 ng/mL (as derived in the PK/PD model). Note that the dosing schedule crosses over at 20 kg and this is represented by the notch in each graph. Under the low dose regimen (10/20), a small fraction would not exceed the threshold concentration (EC₉₀) and hence, potentially underdosed, while under the high dose regimen (20/40) the majority of subjects would exceed this target concentration.

Figure 1: Relation between body weight (BW) and Cav,ss (average concentration at steady state) for each dose strategy



Summary

In summary the study was able to successfully produce a PK/PD analysis that supports the proposed dosing regimen for children above the age of one year and a weight of greater than 8 kg. It found that weight was the main predictor of drug concentration for a particular dose. Furthermore the study showed that using a simple dosing regimen of 10 mg for children < 20 kg and 20 mg for children > 20 kg, the majority of children were likely to have plasma concentrations of Revatio within the therapeutic range.

Efficacy

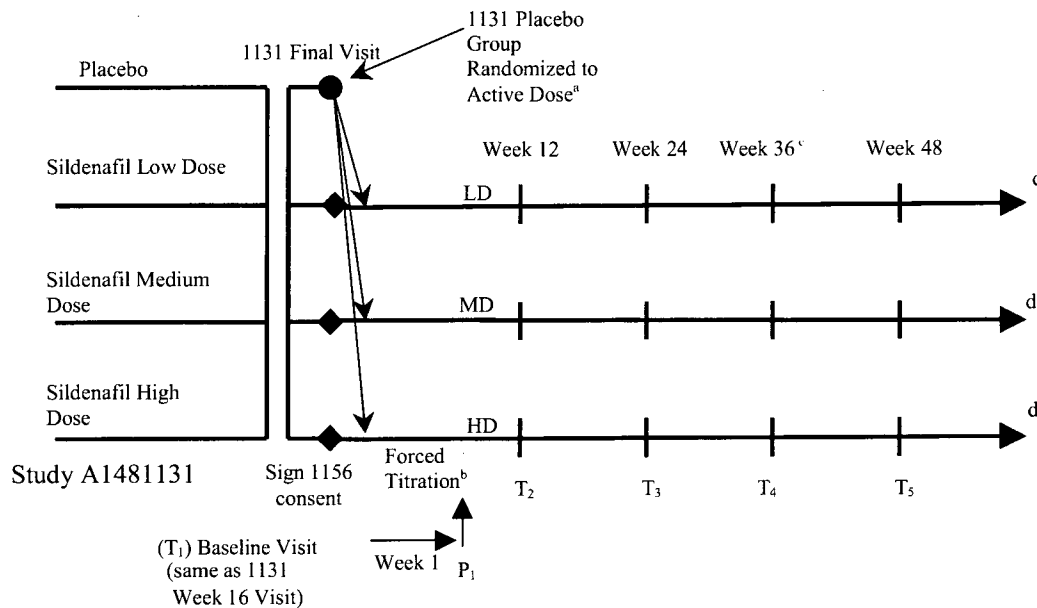
One pivotal study (study A1481131) submitted by the sponsor investigated efficacy of Revatio in the treatment of children with PAH. The sponsor also included a supplemental clinical study report and a follow up safety study (study A1481156) which included some uncontrolled efficacy data.

Study A1481131

Study A1481131 was a multicentre, randomized, double blind, placebo controlled, parallel group, dose ranging study of Revatio in children 1 to 17 years of age with PAH. It was conducted in 32 countries in the Americas, Europe and Australasia. Its prime objective was to study the efficacy and safety of Revatio in children with PAH. The PK component was discussed above.

Children with PAH were allocated to one of 3 Revatio dosing regimens; low, medium, high (Figure 2). There was also a placebo arm. The dose varied between 10 mg and 80 mg tds with at least 6 hours between doses. The dose in each arm was based upon weight and chosen to achieve target maximum drug concentration (C_{max}) of 47, 140 and 373 ng/mL respectively. Patients received either whole tablets or, if they were unable to swallow the tablets, crushed tablets mixed in approximately 5 mL of food. All subjects randomized to sildenafil initially received Revatio 10 mg tds for one week. After one week their sildenafil dose was increased to their randomized dose. Patients allocated to the placebo dose received a dummy escalation schedule. The study was for a total of 16 weeks duration. After that, patients could choose to enter into the extension study A1481156.

Figure 2: Study A1481131 Design



The study was designed to achieve 90% power to detect a 20% treatment difference and allowed for an adjustment for multiple comparisons. The sponsor calculated that 51 subjects per group were required to achieve this. The sponsor provided a complete statistical plan. The primary outcome measure was analysed using an analysis of covariance (ANCOVA) for both the “intention to treat” (ITT) and “per protocol” (PP) populations. Most secondary outcome measures were also analysed by ANCOVA for the ITT population.

Randomisation was stratified by weight and the ability of patients to perform the primary outcome measure: the cardiopulmonary exercise test (see below). In patients > 20 kg, the assignment to the four groups (3 dosing groups and placebo) was 1:1:1:1. In those <20 kg the low and medium dose groups received the same dose and so the assigned groups were 1:1:2 (placebo : medium dose : high dose). Randomisation was achieved using an interactive voice response system (IVRS) assignment. Blinding was maintained by using unidentified tablets including the placebo and an emergency blind breaking system was included in the protocol.

Inclusion Exclusion Criteria

The inclusion criteria included:

- Primary PAH
- Secondary PAH with:
 - Oxygen saturation (SaO₂) ≥ 88% or
 - Transposition of the Great Arteries repaired within the first 30 days of life or
 - Surgical repair of other congenital heart lesions 26 months prior to screening and did not have clinically significant residual left sided heart disease
- Age: 1 to 17 years old
- Weight ≥ 8 kg

These inclusion criteria are consistent with the international classification of pulmonary hypertension. Exclusion criteria included PAH secondary to other diseases, left sided heart disease and other similar heart related diseases, or had treatment with off label sildenafil, an endothelin-A receptor antagonist or prostacyclin/prostacyclin analogue within 30 days prior to randomization or who were taking medications such as parenteral inotropic medication, parenteral vasodilators within 3 months prior to screening, alpha-blockers or CYP3A4 inhibitors. These patients would mostly fall within Group I of the international classification of pulmonary hypertension (PH) consistent with PAH. It was noted that the majority of patients were of WHO functional Class PAH I-III with only 2 patients being Class IV PAH (Table 4:). This probably reflects the limited number of children with this severity of PAH and the difficulty in enrolling these patients in a clinical trial.

Table 4: A1481131 Baseline Efficacy Endpoint Characteristics

	Sildenafil Group				Placebo
	Low	Medium	High	Combined	
Number of subjects (developmentally able only)	24	26	27	77	29
Mean (SD) peak VO ₂ , mL/kg/minute	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Mean (SD) time to peak VO ₂ , seconds	414.54 (123.13)	452.27 (141.88)	433.81 (108.69)	434.04 (124.44)	466.43 (139.14)
Mean (SD) predicted peak VO ₂ , %	43.15 (10.46)	45.32 (12.25)	46.07 (10.84)	44.91 (11.15)	51.16 (12.18)
Number of subjects					
Mean (SD) RER	1.10 (0.07)	1.10 (0.12)	1.09 (0.09)	1.10 (0.09)	1.11 (0.13)
Mean (SD) mPAP, mmHg	66.3 (22.2)	61.9 (18.1)	61.6 (23.9)	62.8 (21.7)	59.4 (21.6)
Mean (SD) PVRI, Wood units*m ²	23.5 (15.2)	19.0 (13.8)	20.9 (19.0)	20.9 (16.6)	16.1 (12.0)
Mean (SD) Cardiac Index, L/minute/m ²	2.95 (1.16)	3.40 (1.85)	3.73 (2.09)	3.44 (1.84)	4.08 (2.31)
WHO Class, n (%)					
I	9 (22.5)	20 ^b (37.0)	21 (27.6)	50 (29.4)	25 (41.7)
II	22 ^b (55.0)	25 (46.3)	43 (56.6)	90 (52.9)	29 (48.3)
III	9 (22.5)	8 (14.8)	12 (15.8)	29 (17.1)	6 (10.0)
IV	0	1 (1.9)	0	1 (0.6)	0
Missing	2	1	1	4	0

SD = standard deviation, RER = respiratory exchange ratio, PVRI = pulmonary vascular resistance index, mPAP = Mean Pulmonary Arterial Pressure, WHO = World Health Organisation

Outcomes

The primary outcome criterion was the percent change in pVO₂ at 16 weeks. The sponsor included pVO₂ as a primary endpoint for each dosing group and was powered to detect a difference between each of these groups and the placebo group. The pVO₂ was measured by a cardiopulmonary exercise test (CPX) which involved the child cycling on a stationary bike through a graded challenge. This differed from the usual adult method of assessing response in PAH which is a 6 minute walk test (6-MWT). In consultation with the EMA (as outlined in the PIP), the sponsor chose the CPX test to measure pVO₂ as it was felt to be more developmentally appropriate. As highlighted in the supplementary report, children less than 7 years and some with developmental difficulties were not able to successfully complete this test and other outcome measures needed to be relied upon. The sponsor compared each of the three dosing groups against placebo as well as the combined dosing group against the placebo group.

The secondary outcome measures included, mean pulmonary artery pressure (mPAP), pulmonary vascular resistance index (PVRI), pulmonary vascular resistance (PVR) and cardiac index, right atrial pressure (RAP), respiratory exchange ratio (RER) and time to pVO₂ as assessed by the CPX test.

Quality of life (QoL) was measured by the physical and psychosocial scales from the Child Health Questionnaire - Parent Form (CHQ-PF28) and WHO PH functional class. Some tertiary outcome measures were also listed.

Results

The analyses provided by the sponsor used the ITT population unless this was otherwise specified.

Demographics

The study screened 325 patients and 235 of these were enrolled. Of these, 228 completed the study and 220 enrolled in the follow up study (study A1481156.). The distribution of patients across treatment groups was not even because no patients with weight less than 20 kg were randomized to the sildenafil low treatment group and the randomisation allocation to sildenafil medium, high and placebo groups was 1:2:1 in this weight group. Some patients that initially failed screening were later rescreened and subsequently randomized: 2 subjects in the sildenafil low group and 3 patients each in the sildenafil medium, high and placebo groups. Approximately 60% of the enrolled patients were female. Their demographic details are shown in Table 5. The percentages of subjects that were developmentally able to exercise in the placebo, low, medium and high dose groups were 50%, 67%, 50% and 38% respectively. These differences can be explained as a result of patients with weight less than 20 kg not being randomised to the sildenafil low group and proportionally more of these patients being randomized to the sildenafil high treatment group compared to the other treatment groups. Approximately one third of patients had primary PAH while the remaining two thirds had secondary causes for their disease. The vast majority of patients completed the study (between 95.2% and 98.7% depending upon assignment group), however, only about half of each group were able to be analysed for the primary outcome measure pVO₂ as shown in Table 6.

Table 5: Demographic Details

Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
Number of subjects	42	55	77	174	60
Male, n (%)	17 (40.5)	24 (43.6)	26 (33.8)	67 (38.5)	22 (36.7)
Female, n (%)	25 (59.5)	31 (56.4)	51 (66.2)	107 (61.5)	38 (63.3)
Age (years), n (%):					
1-4	0	9 (16.4)	19 (24.7)	28 (16.1)	7 (11.7)
5-12	25 (59.5)	28 (50.9)	36 (46.8)	89 (51.1)	37 (61.7)
13-17	17 (40.5)	18 (32.7)	22 (28.6)	57 (32.8)	16 (26.7)
≥18	0	0	0	0	0
Race, n (%):					
White	19 (45.2)	26 (47.3)	28 (36.4)	73 (42.0)	24 (40.0)
Black	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	2 (3.3)
Asian	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Other	18 (38.1)	15 (27.3)	33 (42.9)	64 (36.8)	27 (45.0)
Region, n (%):					
America ^a	10 (23.8)	11 (20.0)	16 (20.8)	37 (21.3)	17 (28.3)
Asia	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Europe	16 (38.1)	18 (32.7)	22 (28.6)	56 (32.2)	16 (26.7)
South America	10 (23.8)	13 (23.6)	24 (31.2)	47 (27.0)	20 (33.3)
Mean weight (range), kg	38.2 (20.0-105.0)	32.1 (8.6-106.0)	25.8 (8.2-61.0)	30.8 (8.2-106.0)	29.3 (9.1-60.0)
Mean height (range), cm	141.6 (111.0-172.0)	130.5 (77.0-192.5)	120.8 (72.0-180.0)	128.9 (72.0-192.5)	128.4 (78.0-173.0)
Mean BMI (SD), kg/m ²	18.2 (4.8)	17.6 (3.9)	16.3 (3.4)	17.2 (4.0)	16.9 (3.6)

BMI=body mass index

^a America=includes USA, Canada and Mexico

Table 6: Subjects excluded from efficacy analysis

Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
Number (%) of subjects:					
Randomized	42	56	77	175	60
Treated	42	55 ^a	77	174 ^a	60
Analyzed for efficacy					
ITT population ^b	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Developmentally able (peak VO ₂)	28 (66.7)	28 (50.0)	29 (37.7)	85 (48.6)	30 (50.0)
Analyzed for primary analysis	24 (57.1)	26 (46.4)	27 (35.1)	77 (44)	29 (48.3)
PP population	23 (54.8)	23 (41.1)	27 (35.1)	73 (41.7)	24 (40.0)
Reason for exclusion from primary analysis ^c					
Discontinued	1 (3.6)	0	1 (3.4)	2 (2.4)	0
Machine failure/damage	1 (3.6)	0	1 (3.4)	2 (2.4)	1 (3.3)
Too ill	1 (3.6)	0	0	1 (1.2)	0
Other ^d	1 (3.6)	2 (7.1)	0	3 (3.5)	0
Reason for exclusion from PP population					
Failed inclusion/exclusion criteria	1 (3.6)	1 (3.6)	1 (3.4)	3 (3.5)	1 (3.3)
Non compliance	0	0	0	0	0
Prohibited concomitant medication	0	0	0	0	0
No baseline or Week 16 VO ₂	5 (17.9)	4 (14.3)	2 (6.9)	11 (12.9)	5 (16.7)
Received incorrect medication	0	1 (3.6)	0	1 (1.2)	0

ITT=intention-to-treat; PP=per protocol

^a Subject 10463 was randomized but not treated

^b Subjects who were randomized to study treatment and received ≥ 1 dose of study treatment

^c All subjects were excluded from the primary analysis because they had a missing Week 16 assessment. The denominator used for percentages was the number of subjects developmentally able to perform the CPX test. Reasons for exclusion from primary analysis are documented in various sources including CRFs

^d Other category included inadequate CPX test result, no staff available at site to run the CPX test or the test was erroneously not done

Primary Efficacy Assessment: Change in pVO₂ at Week 16

The study indicated a dose dependent change in pVO₂ at 16 weeks when compared to baseline. However, the overall improvement did not reach statistical significance ($p=0.056$). The low dose group had a similar small improvement as the placebo (3.81%) while the medium group improved 11.33% and the high dose group improved by 7.98%. The summary of the results are shown in Table 7 and Figure 3. The sponsor also performed some *post hoc* subgroup analyses including those based upon gender, aetiology, disease severity, weight, race and religion, however, the numbers involved were insufficient to draw conclusions. When analysed by disease (primary vs secondary PAH), all groups showed a trend towards a mean improvement in pVO₂ when compared with placebo, however the confidence intervals were too wide to draw any firm conclusions.

Table 7: Percentage Change from Baseline in Peak Volume of Oxygen Consumed (VO₂) at Week 16 (LOCF) - ITT

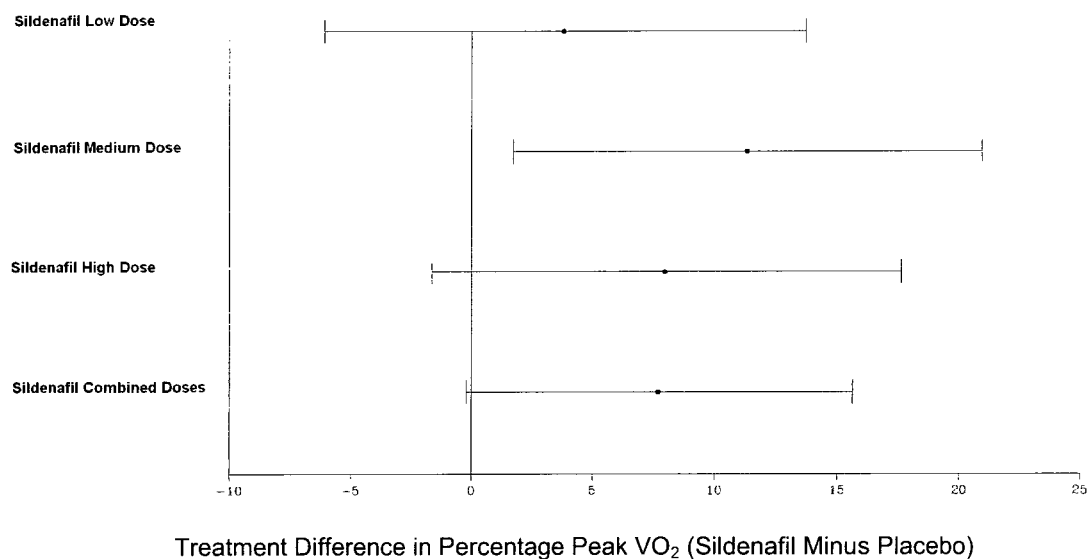
Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
Number of subjects ^a	24	26	27	77	29
Mean (SD) VO ₂ , mL/kg/minute					
Baseline ^b	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Week 16	18.40 (5.61)	20.39 (6.16)	19.00 (3.59)	19.28 (5.21)	20.01 (4.44)
Change from baseline	1.03 (3.41)	2.36 (3.36)	1.57 (2.56)	1.67 (3.13)	-0.01 (3.34)
Percentage change from baseline	6.44 (20.16)	13.40 (19.50)	10.58 (15.51)	10.24 (18.39)	0.53 (15.91)
Mean difference versus placebo (SE) ^c	3.81 (5.00)	11.33 (4.84)	7.98 (4.85)	7.71 (3.98)	NA
95% Confidence interval ^c	-6.11, 13.73	1.72, 20.94	-1.64, 17.60	-0.19, 15.60	NA
P-value ^c	NA	NA	NA	0.056	NA

LOCF=last observation carried forward; ITT=intention-to-treat population; SE=standard error; SD=standard deviation; NA=not applicable

^a ITT subset of developmentally able subjects

^b Baseline was the average of all assessments on or before the first day of study treatment

^c Analyses were performed using analysis of covariance with etiology, weight and baseline peak VO₂ as the covariates

Figure 3: Treatment Difference in Percentage Change from Baseline in Peak VO₂ at Week 16 (LOCF): Mean and 95% Confidence Intervals – ITT

Baseline was the average of all assessments on or before the first day of study treatment

ITT subset of developmentally able subjects

Secondary Efficacy Assessment: Change in mPAP at Week 16

The medium and high dose groups both showed some improvements over placebo. The mean reductions, compared to placebo, were -3.5 mmHg and -7.3 mmHg, respectively. The combined group change, compared to placebo, was -3.1 mmHg with $p = 0.17$, a statistically insignificant result.

Secondary Efficacy Assessment: Change in WHO PH Functional Class at Week 16

All three dose groups showed some improvements over placebo with a change in functional class. Those in Class I were unable to improve their assessment for this parameter and so this secondary outcome measure does not apply to them. The baseline class is shown in Table 8. The odds ratios for the low, medium and high dose groups compared to placebo were 0.6, 2.25 and 4.52, respectively. Not all patients improved over the 16 weeks of the study. At 16 weeks 6 patients (3.4%) of the combined treatment group had worsened by one class. This compared to 4 patients (6.7%) in the placebo group. No patient was reported to change by more than one class.

Table 8: Baseline WHO PH Functional Class

Class, n (%) ^a	Sildenafil				Placebo
	Low	Medium	High	Combined	
I	9 (22.5)	20 ^b (37.0)	21 (27.6)	50 (29.4)	25 (41.7)
II	22 ^b (55.0)	25 (46.3)	43 (56.6)	90 (52.9)	29 (48.3)
III	9 (22.5)	8 (14.8)	12 (15.8)	29 (17.1)	6 (10.0)
IV	0	1 (1.9)	0	1 (0.6)	0
Missing	2	1	1	4	0

WHO=world health organization

^a The number of subjects with known WHO functional class has been used as the denominator for the calculation of percentages

^b Subjects 11620 (sildenafil low dose) and 11221 (sildenafil medium dose) recorded baseline functional class on Day 2. The investigators confirmed that there was no significant change in functional class from pre-treatment and therefore these records were used as the baseline value.

Secondary Efficacy Assessment: Change in Time to pVO₂ at Week 16

Mean baseline time to pVO₂ value were comparable across treatment groups (6.9 to 7.8 minutes). Increases from baseline in mean time to pVO₂ were observed for all sildenafil groups. The sildenafil combined group showed a 9.24% mean increase compared to placebo in change in time to pVO₂ (95% CI: -3.05, 21.54).

Secondary Efficacy Assessment: Change in Cardiac Index at Week 16

Increases from baseline in mean cardiac index were observed for all sildenafil groups. The sildenafil combined group showed an increase compared to placebo in cardiac index of 0.74 L/minute/m² (95% CI: 0.14, 1.34).

Secondary Efficacy Assessment: Change in Pulmonary Vascular Resistance (PVR) at Week 16

Decreases from baseline in mean PVR compared to placebo were observed for the sildenafil medium and high groups; mean treatment differences compared to placebo were -3.4 and -5.5 Wood units, respectively.⁹ The sildenafil combined group showed a decrease in PVR compared to placebo of 2.9 Wood units (95% CI: -7.1, 1.3).

Secondary Efficacy Assessment: Change in Respiratory Exchange Ratio (RER) at Week 16

At Week 16 mean RER values ranged from 1.05 to 1.10, indicating that subjects were generally exercising maximally. However, the range across individuals was 0.7 to 1.6, suggesting that some subjects did not reach maximum exercise.

⁹ One Wood Unit equals the PVR of an average healthy person

Secondary Efficacy Assessment: Change in Right Atrial Pressure (RAP) at Week 16

There were small decreases from baseline in mean RAP compared to placebo (<1.5 mmHg) observed for all sildenafil treatment groups.

Secondary Efficacy Assessment: Change in Quality of Life (QoL) at Week 16

Increases from baseline in the mean CHQ-PF28 (Child Health Questionnaire – Parent Reported¹⁰) physical and psychosocial scale scores were observed in all treatment groups, including placebo. There was no apparent difference between the sildenafil treatment groups and placebo.

Summary

In summary, study A1481131 provides evidence of a trend towards improvement in clinically relevant parameters over the 16 weeks of the study. The evaluator agreed with the conclusion of the sponsor that the changes in pVO₂ are consistent with an improvement in aerobic exercise tolerance; however, the study was unable to demonstrate this to a statistically significant level. This conclusion is also limited by the fact that younger children (< 7 years) and those with disabilities were unable to be assessed for the primary endpoint. Overall only 44% of patients in the treatment group were able to complete the primary outcome measure and this is a significant deficiency in these data.

Clinical exercise tolerance data are important in assessing the current functional level of a child with PAH. It is recognized that younger children (< 7 years) and those with significant physical disabilities may be unable to validly and repeatedly perform the pVO₂. In these cases, haemodynamic measures including pulmonary vascular resistance and cardiac pressures are important surrogates for PAH status. The evaluator acknowledged that these secondary endpoints suggested haemodynamic improvements over the 16 week study, however these were not statistically significant (and the study was not powered accordingly). Also, as far as the evaluator could determine, the PIP did not include these as alternative primary endpoints for patients who could not complete the PVO₂ test. The EU guidelines for the investigation of PAH were followed in this study except, as mentioned above, for assessing the primary endpoint for exercise tolerance (where the study used the PVO₂ rather than the 6-MWT). The evaluator accepted that this is appropriate for a non-disabled paediatric population over the age of 7 years. The EU PAH guidelines are silent on the appropriate assessment of children. It may have been more appropriate to include a combined primary outcome measure including improvement in exercise capacity and time to clinical worsening; this would have been consistent with the EU PAH guidelines and could have allowed the study design to be more flexible in assessing children of different developmental stages.

Finally, the differences found between the groups were smaller than those anticipated in the power calculation (which was 20%), hence if the described differences were significant, the study was underpowered to detect them and this was exacerbated by the large number of patients who were unable to fully complete the study's primary outcome measure.

Study A1481131 Supplemental Clinical Study Report

The sponsor submitted a supplementary report to address the issue that a significant number of participants in Study A1481131 were unable to complete the CPX to assess their pVO₂, the primary endpoint.

¹⁰ This questionnaire is a widely used and validated measure for assessing QoL in children.

Study subgroup

The details of the study subgroups are shown in Table 9. The sponsor divided the patients into 3 groups:

- <7 years old;
- >7 years old and not developmentally able (NDA);
- >7 years old and developmentally able (DA) (that is, the developmentally able population used in study A1481131)

Table 9: Study A1481131 Study subgroup

Number (%) of subjects:	Sildenafil Dose				Placebo
	Low	Medium	High	Combined	
Randomized	42	56	77	175	60
ITT ¹	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Etiology					
a. PPH	12 (28.6)	19 (34.5)	26 (33.8)	57 (32.8)	21 (35.0)
b. surgical repair	14 (33.3)	16 (29.1)	25 (32.5)	55 (31.6)	16 (26.7)
c. shunt	16 (38.1)	20 (36.4)	26 (33.8)	62 (35.6)	23 (38.3)
Age and developmental ability					
a. < 7 year	2 (4.8)	17 (30.9)	28 (36.4)	47 (27.0)	16 (26.7)
b. ≥ 7 year NDA	12 (28.6)	10 (18.2)	20 (26.0)	42 (24.1)	14 (23.3)
c. ≥ 7 year DA	28 (66.7)	28 (50.9)	29 (37.7)	85 (48.9)	30 (50.0)
Excluding subjects with congenital systemic-to-pulmonary shunt					
a. Overall	26 (61.9)	35 (63.6)	51 (66.2)	112 (64.4)	37 (61.7)
b. < 7 year	2 (4.8)	12 (21.8)	21 (27.3)	35 (20.1)	12 (20.0)
c. ≥ 7 year NDA	7 (16.7)	5 (9.1)	10 (13.0)	22 (12.6)	7 (11.7)
d. ≥ 7 year DA	17 (40.5)	18 (32.7)	20 (26.0)	55 (31.6)	18 (30.0)

¹ Subjects who were randomized to study treatment and received ≥1 dose of study treatment. Denominators for the subgroup percentages are based on the ITT population.

The sponsor then reanalysed the outcomes by group to investigate whether those unable to complete the CPX were different on any of the other outcome measures from those that were able to complete the primary outcome measure. Given the circumstances, this is a reasonable approach to address the issue. The deficiency in this approach is that the study was never powered for this sub-analysis and the conclusions will, necessarily, be limited by the relatively small number of patients in each subgroup. The sponsor also analysed the data by disease aetiology and reanalysed the data with the exclusion of patients with congenital systemic to pulmonary shunts (Table 9). While these data are of some interest, they add little to the information obtained in the full study.

Results

Demographics

There were a total of 47 patients in the < 7 year age group and 42 in the > 7 year NDA group making a total of 87 patients or 51% of the total patient number who received the active drug. Likewise, in the placebo group, 30 (50%) of the 60 patients were unable to perform the primary outcome. As patients < 20 kg were not randomized into the low dose group, only 2 patients from the < 7 year group received low dose Revatio. This is a significant deficiency in the study.

Secondary Efficacy Assessment: Haemodynamic Assessment

The sponsor's *Clinical Study Report* has not given a full consideration of the implications of the missing primary endpoint assessment. The sponsor has fully described the deficiency as detailed below (see Figures 4, 5 and 6):

Subjects in the <7 year subgroup had lower mean mPAP and PVRI values at baseline than the other subgroups. In this subgroup mean changes from baseline, in comparison to placebo, were small with mPAP, PVRI and Cardiac Index. As there were only 2 evaluable subjects in the low dose group with this subgroup only the medium and high dose groups are potentially interpretable.

As there were at most 12 evaluable subjects in the placebo group with the >7 year NDA subgroup, comparisons across active dose groups with respect to differences from placebo may be strongly influenced by this small group size. For example, there appears to be a dose relationship with mPAP, however, following adjustment for placebo there is a mean increase in mPAP with all three active dose groups. Mean increases from baseline in Cardiac Index, compared to placebo, were observed with all three active dose groups (range 2.1 to 2.4 L/min/m²).

Figure 4: Change in mPAP from Baseline (Excluding Subjects with Congenital Systemic-to-Pulmonary Shunts) by Age and Developmental Ability

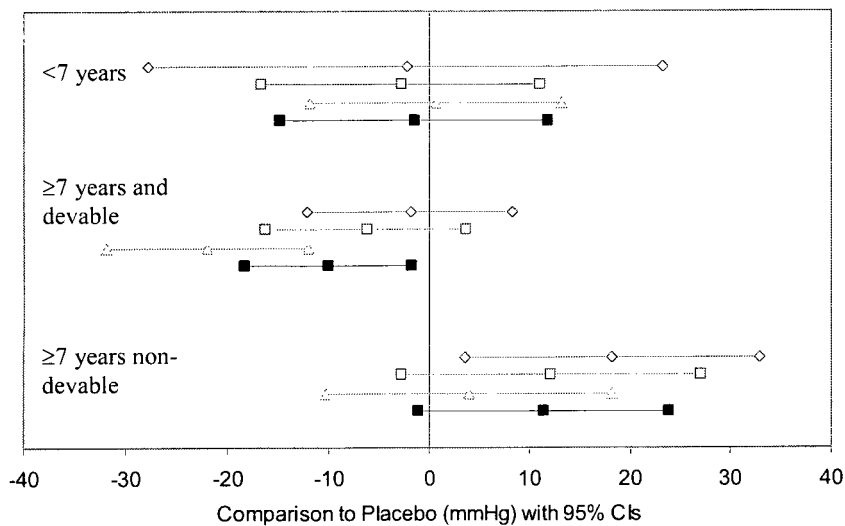
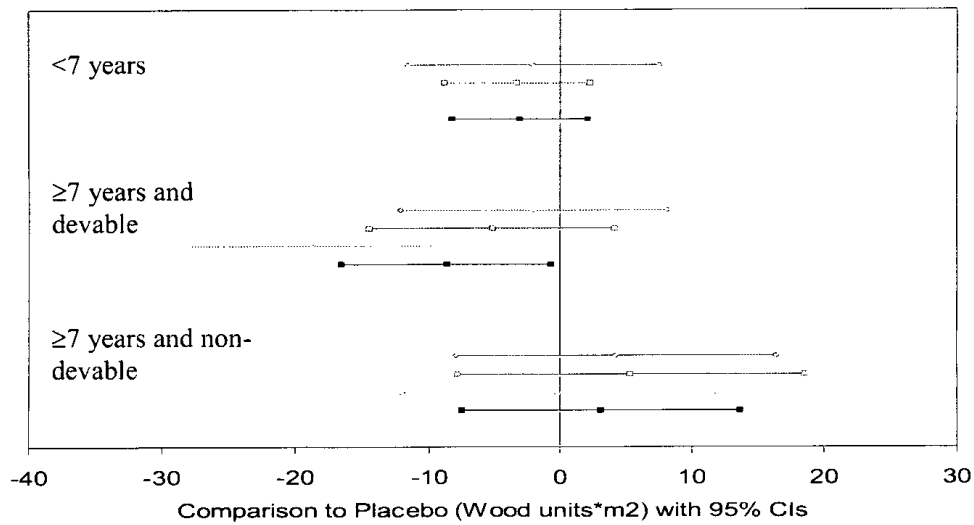
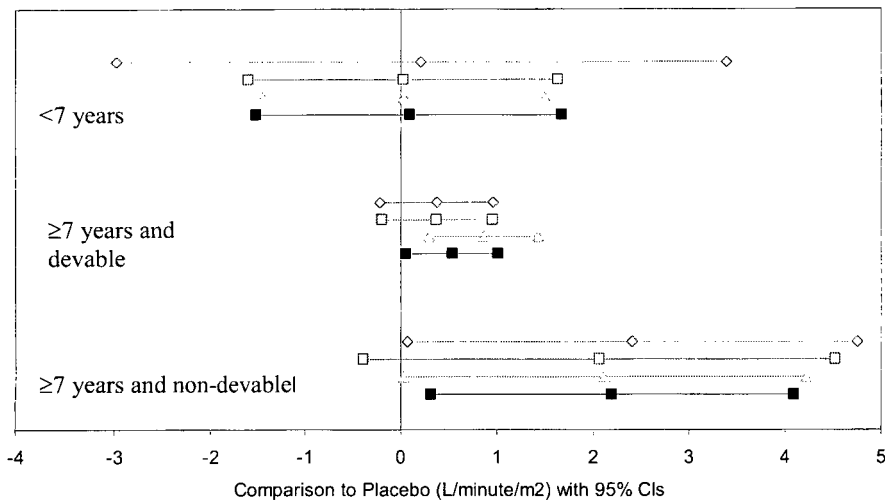


Figure 5: Change in PVRI from Baseline (Excluding Subjects with Congenital Systemic-to-Pulmonary Shunts) by Age and Developmental Ability



◇ Low dose; □ Medium Dose; △ High Dose; ■ Combined sildenafil; Devable= Developmental ability; CIs = Confidence incidences

Figure 6: Change in Cardiac Index from Baseline (Excluding Subjects with Congenital Systemic-to-Pulmonary Shunts) by Age and Developmental Ability



◇ Low dose; □ Medium Dose; △ High Dose; ■ Combined sildenafil; Devable= Developmental ability; CIs = Confidence incidences

Figure 4, Figure 5 and Figure 6 show the summary data for some of the secondary haemodynamic outcome measures evidence in the groups that were excluded from the primary analysis (< 7 year and the > 7 year NDA groups). These subgroups do not show as favourable haemodynamic changes as the > 7 year group. The evaluator was unsure as to why this group failed to demonstrate the expected improvement and speculated whether

this was a developmental issue, in that these children were less responsive to Revatio or whether a larger study may have detected a difference. This should be addressed in detail by the sponsor. However, based on the available data, the evaluator could not recommend the use of Revatio in children < 7 years of age.

Secondary Efficacy Assessment: Change in WHO PH Functional Class at Week 16

A greater proportion of subjects in the >7 year DA subgroup (23/112, 21%) had WHO FC III or IV at baseline than the other two age and ability subgroups (< 7 year (6/63, 10%) and >7 year NDA (7/55, 13%)). Of those in the >7 year DA subgroup 20/82 (24%) received sildenafil and 3/30 (10%) received placebo. No subjects with WHO FC II-IV at baseline deteriorated (Table 10). Of those subjects WHO FC I at baseline none in the >7 year NDA subgroup deteriorated, whilst 5 subjects deteriorated in both the < 7 year and >7 year DA subgroups.

Table 10: Study A1481131 Improvement in WHO FC for Subjects WHO FC II-IV at Baseline by Ability Group

Subgroup	Treatment	N	n (%)
< 7 year	Placebo	7	0
	Sildenafil	29	7 (24)
≥7 year NDA	Placebo	8	2 (25)
	Sildenafil	28	5 (18)
≥7 year DA	Placebo	20	2 (10)
	Sildenafil	63	21 (33)

Secondary Efficacy Assessment: Change in QoL at Week 16

No improvements were demonstrated in the subgroup analysis (compared to placebo). The sildenafil combined group changes from baseline in CHQ-PF28 Physical and Psychosocial Scale Scores at Week 16 (for the aetiology or age and ability subgroups) were similar to that in the placebo group.

Other subgroup analyses

The sponsor also performed subgroup analyses based upon aetiology, the results of which add little to the study interpretation.

Summary

In summary, study A1481131 supplementary report attempted to address the implications of the primary endpoint not being assessable in 51% of the ITT population. While there is a trend to improvements in the secondary endpoints, the sub-analysis is unclear as to whether those groups excluded from the primary endpoint analysis (<7 year and the >7 years NDA groups) are different to those who were able to be assessed for the primary outcome measure (≥ 7 years DA group). The extra analysis fails to address the fundamental deficiency in design; in that a large subgroup of patients, that is those < 7 years of age and those with developmental problems were unable to be assessed for the nominated primary outcome measure (pVO₂). Furthermore, the *post hoc* analysis of the secondary outcome measures was unable to demonstrate a clinically significant benefit of Revatio for any of these outcomes.

Study A1481156

Study A1481156 was a multicentre, long term extension study enrolling all subjects with PAH who completed a 16 week, placebo controlled study A1481131. The study was initially blinded until study A 1481131 was completed. Study A1481156 then continued in an open label fashion. The study is ongoing; this being an interim analysis. Patients were maintained in their study A 1481131 group except for placebo. Patients in the placebo group were re-randomised in to the active groups as per study A1481131. A total of 220 patients were enrolled from study A1481131.

Outcomes

The primary outcome was safety. However, the study included some efficacy assessments:

- pVO₂ CPX Test
- WHO functional class for PAH
- Change in Background Therapy
- Subject/parent and physician global assessments
- CHQ-PF28 questionnaire

Results

Across studies A1481131 and A1481156, the duration of treatment for individual subjects ranged from 3-1815 days. The median duration of treatment ranged from 767-1014 days (excluding subjects who received placebo in A1481131 that were not randomized to treatment in A1481156). Overall, 206 (88.0%), 129 (55.1%), and 88 subjects (37.6%) were treated for at least 1, 2 and 3 years, respectively corresponding to 206/234 (88.0%), 129/173 (74.6%) and 88/133 (66.2%) of those subjects who had the potential to reach 1, 2 and 3 years duration did so, respectively.

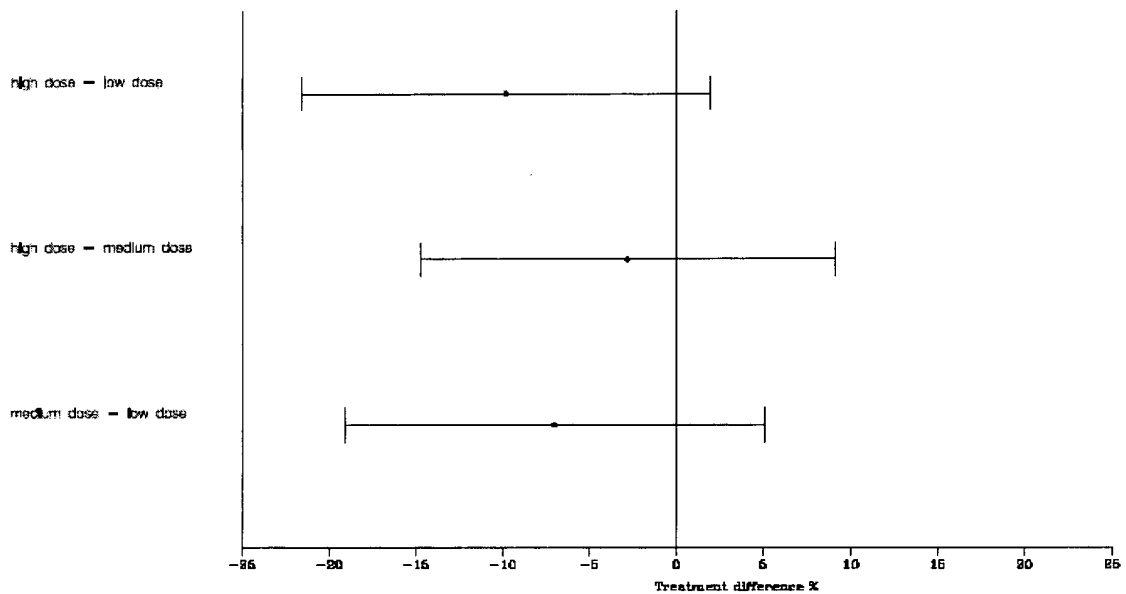
For the 60 subjects who were randomized to placebo in A1481131, duration of treatment with sildenafil in A1481156 ranged from 2 to 1679 days, with the median duration being greater for the low dose (901 days) compared to the medium and high doses (592 and 672 days, respectively).

Change in pVO₂ at 1 year

All 3 groups maintained a higher pVO₂ at 1 year when compared to baseline (Table 11), however, there was significant overlap between the groups (Figure 7).

Table 11: Percentage change from Baseline in Peak Volume of O₂ consumed (pVO₂) at 1 year - ITT

	Sildenafil Low Dose (N=33)	Sildenafil Medium Dose (N=32)	Sildenafil High Dose (N=35)
Baseline			
Mean (SD)	18.30 (4.54)	18.11 (4.44)	17.78 (3.65)
Year 1			
Mean (SD)	19.97 (5.17)	18.69 (5.92)	17.93 (4.02)
Mean (SD) Change from Baseline	1.67 (3.64)	0.58 (5.22)	0.15 (3.44)
Mean (SD) % Change from Baseline	11.19 (22.98)	5.37 (31.62)	2.56 (21.46)
Comparison with Low Dose:			
Mean Difference (SE)		-7.02 (6.10)	-9.84 (5.92)
95% Confidence Interval		-19.13, 5.09	-21.60, 1.93
p-value		0.253	0.100
Comparison with Medium Dose:			
Mean Difference (SE)			-2.82 (6.01)
95% Confidence Interval			-14.75, 9.11
p-value			0.640

Figure 7: Treatment Difference in Percentage Change from Baseline in Peak VO₂ at 1 year: Mean and 95% Confidence Intervals - ITT

Change in WHO PH Functional Class

The percentage of subjects showing maintenance (no change or improvement) were similar for all sildenafil dose groups at Year 1 (range 67% - 76%) and at Year 3 (range 46% - 50%). As the sponsor noted, these data should be interpreted with caution as all discontinuations and missing values are taken as deteriorations.

Summary

The interim analysis of study A1481156 lends support to the sponsor's assertion that there may be ongoing therapeutic benefit for patients with long term sildenafil therapy,

with the majority of subjects displaying maintenance (and potentially improvement in some) with pVO₂ and WHO functional class. The evaluator agreed with the sponsor that there were no data to indicate any added benefit with efficacy of higher doses of sildenafil compared to lower doses.

Summary of Efficacy

In summary, study A1481131 and its extension, study A1481156, provided evidence of a trend towards improvement in clinically relevant parameters over the 16 weeks of the study. The evaluator agreed with the sponsor's conclusion that the changes in pVO₂ are consistent with an improvement in aerobic exercise tolerance; however, the study was unable to demonstrate this to a statistically significant level. The studies are limited by the fact that younger children (< 7 years) and those with disabilities were unable to be assessed for the primary endpoint. The secondary endpoints also suggested haemodynamic improvements or stability over the period studied. The numbers were insufficient for subgroup analyses to confirm whether certain groups may have a greater benefit from treatment. Based upon the follow up study, there does not appear to be any added efficacy benefit of higher doses of sildenafil compared to lower doses. This lack of dose response was not adequately explained in the submission. The sponsor should address the reasons for the lack of dose response and whether this is explained, at least in part, by the PK/PD modeling. The proposed PI includes a range of doses for children based upon weight consistent with the low dose included in the efficacy studies:

"The recommended dose in patients < 20 kg is 10 mg (1 mL of compounded suspension) three times a day and for patients > 20 kg is 20 mg (2 mL of compounded suspension or 1 tablet) three times a day."

Safety

The sponsor included two study reports which included safety data relevant to the application. These were from studies A1481131 and A1481156. The safety data for study A1481131 was then integrated into the report for study A1481156. The other study reports in the submission involved adult volunteers and did not contain safety data relevant to the proposed treatment population. The sponsor's *Safety Report* also included two extra paediatric studies (Study A1481134 and A1481157) which were reported to have been stopped early due to poor recruitment. The study reports were not included in the submission. A brief summary of these two studies, from the safety report, is included below; however the data cannot be verified.

Exposure

The total exposure for patients enrolled in the pivotal study (A1481131) and its follow up study (A1481156) are shown in Table 12. The submission stated that overall, in studies A1481131/A1481156 combined 206/234 patients (88%) have received ≥1 year of therapy (from the start of Study A1481131), 129 (59%) have received ≥2 years of therapy and 88 (20%) have received ≥3 years of therapy (for the 60 placebo treated subjects in A1481131, this includes 12 weeks of placebo treatment). This corresponds to 206/234 (88.0%), 129/173 (74.6%) and 88/133 (66.2%) of those subjects who had the potential to reach 1, 2 and 3 years duration, respectively.

Table 12: Total Exposure for children presented in the submission

Study type	Number of patients			
	Total Exposed	With long term safety data		
		≥1 year	≥2 years	≥3 years
Placebo-controlled Study A 1481131 /A 1481156	234	206	129	88

Study A1481156

Study A1481156 was a multicentre, long term extension study enrolling all subjects with PAH who completed a 16 week, placebo controlled study A1481131. The study was initially blinded until study A 1481131 was completed. Study A1481156 then continued in an open label fashion. This report is an interim analysis with the data cut-off 15 May 2009. The report also covered adverse events (AEs) from the preceding efficacy study A1481131. The safety outcomes include:

- Adverse events
- Vital signs
- Survival Status
- Clinical Examination
- Clinical laboratory tests
- Electrocardiogram (ECG)
- Ocular Tests
- Paediatric Development

Adverse Events

Every patient (100%) experienced at least 1 AE. Treatment related AEs were reported for between 26.1% and 53.8% of subjects in each treatment arm. Most AEs were mild or moderate in severity. The submission stated that the most common all causality AEs with those subjects who received sildenafil were upper respiratory tract infection (URTI; 25.3%), headache (23.1%) and vomiting (22.7%). Some AEs (for example, URTI, nausea, pneumonia) had a higher incidence in the medium and high dose groups compared to the low dose groups. The most common treatment related AEs with those subjects who received sildenafil were headache (13.1%) and vomiting (6.6%). An overall summary of the AE incidence and commonly reported treatment emergent AEs are shown in Table 13 and Table 14.

Table 13: Overall Summary of Incidence of Adverse Events by A1481131/A1481156 Treatment Sequence

Number (%) of Subjects	Sildenafil Low/ Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non- Randomized
All Causalities							
Evaluable for AEs	42	55	77	13	19	23	5
Number of AEs	225	347	471	77	101	92	12
With AEs	39 (92.9)	52 (94.5)	66 (85.7)	13 (100)	19 (100)	19 (82.6)	3 (60.0)
With SAEs	9 (21.4)	22 (40.0)	30 (39.0)	1 (7.7)	3 (15.8)	6 (26.1)	0
With Severe AEs	6 (14.3)	18 (32.7)	25 (32.5)	2 (15.4)	1 (5.3)	3 (13.0)	1 (20.0)
Discontinued due to AEs	1 (2.4)	4 (7.3)	4 (5.2)	1 (7.7)	1 (5.3)	1 (4.3)	0
With Dose Reduced or Temporary Discontinuation due to AEs	6 (14.3)	7 (12.7)	13 (16.9)	1 (7.7)	3 (15.8)	0	1 (20.0)
Treatment-Related							
Evaluable for AEs	42	55	77	13	19	23	5
Number of AEs	38	48	89	15	13	13	11
With AEs	14 (33.3)	20 (36.4)	29 (37.7)	7 (53.8)	6 (31.6)	6 (26.1)	3 (60.0)
With SAEs	1 (2.4)	0	3 (3.9)	0	0	1 (4.3)	0
With Severe AEs	0	2 (3.6)	5 (6.5)	0	0	2 (8.7)	1 (20.0)
Discontinued due to AEs	1 (2.4)	0	2 (2.6)	1 (7.7)	0	0	0
With Dose Reduced or Temporary Discontinuation due to AEs	1 (2.4)	1 (1.8)	6 (7.8)	0	0	0	1 (20.0)

AE = adverse event; SAE = serious adverse event

Table 14: Summary of Most Frequent Adverse Events (in at Least 10% of Subjects in any Sequence) by Preferred Term by A1481131/A1481156 Treatment Sequence (All Causalities)

Number (%) of Subjects	All (N=234)	Sildenafil Low/ Low Dose (N=42)	Sildenafil Medium/ Medium Dose (N=55)	Sildenafil High/ High Dose (N=77)	Placebo/ Low Dose (N=13)	Placebo/ Medium Dose (N=19)	Placebo/ High Dose (N=23)	Placebo Non- Randomized (N=5)
Page 1 of 2								
Upper respiratory tract infection	58 (24.8)	6 (14.3)	16 (29.1)	22 (28.6)	2 (15.4)	5 (26.3)	7 (30.4)	0
Headache	54 (23.1)	10 (23.8)	12 (21.8)	17 (22.1)	6 (46.2)	3 (15.8)	5 (21.7)	1 (20.0)
Vomiting	53 (22.6)	13 (31.0)	11 (20.0)	21 (27.3)	2 (15.4)	1 (5.3)	4 (17.4)	1 (20.0)
Bronchitis	41 (17.5)	8 (19.0)	11 (20.0)	15 (19.5)	0	4 (21.1)	3 (13.0)	0
Pharyngitis	37 (15.8)	12 (28.6)	7 (12.7)	9 (11.7)	2 (15.4)	4 (21.1)	3 (13.0)	0
Pyrexia	34 (14.5)	6 (14.3)	11 (20.0)	14 (18.2)	0	2 (10.5)	1 (4.3)	0
Nasopharyngitis	32 (13.7)	7 (16.7)	6 (10.9)	8 (10.4)	3 (23.1)	3 (15.8)	5 (21.7)	0
Cough	31 (13.2)	4 (9.5)	11 (20.0)	10 (13.0)	3 (23.1)	1 (5.3)	2 (8.7)	0
Diarrhea	30 (12.8)	4 (9.5)	7 (12.7)	11 (14.3)	4 (30.8)	2 (10.5)	2 (8.7)	0
Rhinitis	19 (8.1)	3 (7.1)	6 (10.9)	7 (9.1)	1 (7.7)	2 (10.5)	0	0
Dizziness	18 (7.7)	4 (9.5)	2 (3.6)	6 (7.8)	2 (15.4)	1 (5.3)	3 (13.0)	0
Epistaxis	18 (7.7)	2 (4.8)	7 (12.7)	6 (7.8)	0	3 (15.8)	0	0
Tonsillitis	18 (7.7)	5 (11.9)	2 (3.6)	7 (9.1)	1 (7.7)	1 (5.3)	2 (8.7)	0
Influenza	16 (6.8)	0	5 (9.1)	4 (5.2)	4 (30.8)	0	3 (13.0)	0
Chest pain	15 (6.4)	2 (4.8)	1 (1.8)	8 (10.4)	2 (15.4)	1 (5.3)	1 (4.3)	0
Dyspepsia	15 (6.4)	4 (9.5)	4 (7.3)	5 (6.5)	0	2 (10.5)	0	0
Nausea	15 (6.4)	1 (2.4)	5 (9.1)	8 (10.4)	1 (7.7)	0	0	0
Pneumonia	15 (6.4)	1 (2.4)	5 (9.1)	5 (6.5)	0	2 (10.5)	2 (8.7)	0
Abdominal pain	14 (6.0)	1 (2.4)	2 (3.6)	8 (10.4)	2 (15.4)	0	1 (4.3)	0
Conjunctivitis	13 (5.6)	2 (4.8)	1 (1.8)	6 (7.8)	1 (7.7)	2 (10.5)	1 (4.3)	0
Syncope	13 (5.6)	4 (9.5)	6 (10.9)	1 (1.3)	1 (7.7)	1 (5.3)	0	0

N = number of subjects

Adverse events reported for >10% of subjects in 1 or more treatment sequence (except for placebo/non-randomized) are presented in order of decreasing frequency.

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. Any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild.

Includes data up to 7 days after last dose of study drug.

Overall 12 patients discontinued from the study due to AEs. AEs that were considered to be related to the study drug included episodes of weight decrease, stridor, dyspnoea, hypoxia and rash macular. The sponsor reported that there were additional discontinuations that were not reported as AEs but which could be considered to be AEs. In one subject (sildenafil high/high dose), due to the poor condition of the subject, it was decided to start treatment with bosentan, a prohibited medication, and stop the study

treatment to avoid a protocol violation and in another subject (sildenafil high/high dose) disease progression was experienced.

Deaths

A total of 22 deaths were reported in this study. Seventeen of them were based on the safety database and another 5 deaths were reported when not on treatment and briefly mentioned below. As far as the evaluator could assess, none of the deaths were attributable to the study medication. Most of the deaths were due to progression or complications of patients underlying cardiovascular disease. The five deaths described below occurred a considerable time after the patients ceased the study medication and so are unlikely to be related.

Serious Adverse Events (SAEs)

Overall, 31% of subjects who received sildenafil at some point in the study experienced at least one SAE. A total of 6 subjects had SAEs that were considered to be related to treatment by the investigator and/or the sponsor (Table 15). The evaluator agreed with the sponsor's assessment of the SAEs relationship to the study medication.

Table 15: Treatment Related Serious Adverse Events

Subject Number	Sex/Age	Preferred Term	Onset Day	Action	Outcome	Investigator/ Sponsor Causality
Sildenafil Medium/Medium Dose						
10432	F/5 years	Convulsion	358	Withdrawn	Recovered/ Resolved	Related/ Related
Sildenafil High/High Dose						
10420	M/20 months	Hypersensitivity	2	Withdrawn	Recovered/ Resolved	Related/ Related
		Stridor	2	Withdrawn	Recovered/ Resolved	Unrelated/ Related
11202	F/9 years	Hypoxia	379	Withdrawn	Recovered/ Resolved	Related/ Related
12001	M/14 years	Ventricular arrhythmia	54	Dose not changed	Recovered/ Resolved	Related/ Unrelated
Placebo/High Dose						
10827	M/10 years	Respiratory tract infection	703	Unknown	Unknown	Related/ Related
10856	F/9 years	Death	815	Withdrawn	Fatal	Unrelated/ Related

M = male; F = female
Age as at screening.

Laboratory Results

Overall there were no significant trends in the laboratory findings over the study. The sponsor reported that 73.2% of subjects had at least one abnormality where the baseline was within the normal range. The most common abnormality was basophils (absolute) >1.2 x the upper limit of normal, in 41.6% of patients.

Vital Signs

There were no significant changes in mean or median sitting blood pressure and heart rate for any of the treatment sequences. Some individual patients did have changes in blood pressure as part of their underlying cardiac disease. Two patients reported episodes of supraventricular tachycardia (SVT).

Electrocardiograms

ECG data were only collected during A1481 131 and changes were consistent with the underlying disease. Two patients reported episodes of SVT; neither of these was considered treatment related.

Weight and Height

Weights and heights were collected over the time of the study and both increased with time.

Physical Examination

Cardiac abnormalities were noted in most patients at baseline; this is expected given the population studied. There were no other significant changes reported over the period of the study.

Paediatric Cognitive Development Assessment

No particular abnormal trends were noted in cognition over the course of the study. Several patients had evidence of developmental disability at baseline; this is not unexpected given the population studied.

Paediatric Motor Development

For the majority of patients, motor development was not limited and there were no apparent treatment effects upon this.

Ocular Measurements

Five subjects had a worsening of their colour vision from baseline. These findings were reported as AEs for three subjects 10416 with two cases of chromatopsia (both mild and considered treatment related) and one case of colour vision tests abnormal (mild but not considered to be treatment related).

Study A1481134 (from Safety Summary)

This was planned as a randomised, multicentre, double blind, placebo controlled, dose ranging, parallel group study to be conducted in approximately 252 subjects (63 per treatment group), aged 0 (> 34 weeks gestational age) to 17 years, receiving one of three doses of IV sildenafil or placebo for a minimum of 24 hours to assess the efficacy of IV sildenafil on pulmonary hypertension during the postoperative period in children with congenital heart disease who have undergone corrective cardiac surgery. Of 87 subjects that were screened, 18 subjects were randomised and 17 were treated. Four of the 17 treated subjects, two each on sildenafil (17%) and placebo (40%), received additional therapy for treatment of postoperative pulmonary hypertension within 24 hours of the start of the study drug infusion. Eight of the 17 subjects, 5 on sildenafil (42%) and 3 on placebo (60%), received additional therapy for pulmonary hypertension to Day 28 follow up. Of the 17 treated subjects, 88.2% reported AEs; none were regarded as possibly treatment related. The most commonly reported AE was pulmonary hypertension due to the disease under study. Two of the treated subjects discontinued; one subject (placebo) died due to pulmonary hypertension related to the disease under study and one subject (medium dose) was withdrawn during active treatment due to lack of efficacy.

Six subjects reported severe AEs and two subjects reported serious treatment emergent AEs. Ten subjects reported non-treatment emergent SAEs (events that occurred more than 7 days after the end of treatment). One subject reported temporary discontinuation of the study drug due to severe pulmonary hypertension aggravated by the disease under study. Four deaths were reported, two occurred pre-randomisation and two occurred in subjects receiving placebo.

Study A1481157 (from Safety Summary)

The study was planned as a two part study. Part 1 was a seven day, open label, multicentre pharmacokinetics study; its primary objective was to evaluate the pharmacokinetics of IV sildenafil in near term and term newborns with persistent pulmonary hypertension of the newborn (PPHN) or with hypoxic respiratory failure and at risk for PPHN. The pharmacokinetic results of Part I were to be used to determine doses and infusion rates for the Part 2 of the study. However, Part 2 of the study was not performed. A total of 36 neonatal subjects with PPHN or hypoxic respiratory failure and at risk of developing PPHN were recruited. Six (17%) subjects completed the seven day treatment period without the need for standard therapy (inhaled nitric oxide [iNO] or extracorporeal membrane oxygen [ECMO]). Furthermore, they remained in the study until Day 28 without the need for any standard therapy. The rest of the subjects [30 subjects (83%)] all started iNO prior to study treatment. The summary states that one patient died, 4 patients discontinued due to treatment emergent AEs and that 20 subjects had a total of 41 treatment emergent, all causality AEs.

Summary on Safety

Overall, the reported safety in the submission is consistent with the known adverse event profile of sildenafil. The adult volunteer studies did not reveal any new or unexpected AEs in that population. The overall type and incidence of AEs in the paediatric population was consistent with those reported in adults. The evaluator did not identify any unexpected treatment emergent adverse events.

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

The evaluator suggested that the following questions need to be addressed:

In the PK component of Study A1481131, the final modelling data suggests that a proportion of children treated with the proposed dosing schedule (10/20) may be under dosed (see Figure 2). Is this in fact true and if so, what proportion of children may be under dosed for different weights? Based upon the PD modeling and the results of the efficacy study, is an alternative strategy (for example dose/kg) potentially a more appropriate approach to dosing?

Efficacy

The evaluator suggested that the following questions need to be addressed:

Could the sponsor confirm that all of the enrolled patients had PAH within the definition of the international classification of PH?

Could the sponsor further clarify the reasons for the apparent lack of dose response in that higher doses did not appear to be related to greater changes in efficacy parameters in Study A1481131? Is this explained, at least in part, by the PK/PD modelling?

Could the sponsor address whether the Study A1481131 was underpowered to detect statistically significant differences between the treatment and placebo groups?

The concerns about the efficacy data in children <7 years have been identified (both functional and haemodynamic parameters). How does the sponsor propose to address this deficiency in the data for this age group? Are there other data that could be presented that demonstrate a benefit in this group?

Clinical Summary and Conclusions

Benefits

Revatio is claimed to be of benefit in the treatment of PAH in children. The data supplied demonstrated a trend to improvement in both the functional and haemodynamic parameters in children >7 years of age when compared to the placebo group. There were however, no demonstrable differences in quality of life data between the groups.

In children <7 years of age, the data did not demonstrate a benefit in either function or haemodynamic parameters in the treatment groups (either individual or combined) when compared to placebo.

Risks

The evaluator did not identify any new or unexpected treatment emergent adverse events. However, given the potential for ongoing long term exposure in children as they develop, the evaluator suggested the continuing surveillance of this patient group who are treated with Revatio.

Balance

The evaluator found that in children over 7 years of age that there is adequate evidence of benefit in the use of Revatio in the treatment of PAH when compared to the identified risks. However, the evaluator found that, in children less than 7 years of age, that there was inadequate evidence of either functional or haemodynamic improvement and so, in these children, the known risks of Revatio outweigh any potential benefit.

Conclusions

Overall, the submission was of reasonable quality and the data support the use of Revatio to be extended to children aged 7 to 17 years with PAH. The data are less complete in children aged 1 to 7 years and a more restrictive statement on efficacy is warranted in this case. The sponsor should provide either further data or evidence that the secondary endpoints used in the pivotal study are appropriate as primary endpoints for this population. The evaluator agreed with the sponsor that data are lacking in children less than 1 year of age. The evaluator acknowledged that the age break points included in the pivotal study are different to those recommended in the EU guidance (these being 28 days to 23 months and 2 to 11 years). However the break point of 7 years in the study appears to be data driven rather than by the sponsor not following the EU guidance.

In terms of WHO class of PAH, the majority of patients were Class I-III. In the pivotal study, only 2 patients had Class IV and so definitive conclusions cannot be drawn on this severely affected group. However, the evaluator did not believe that children Class IV PAH should be excluded from having access to Revatio.

The evaluator believed that there were currently adequate safety data to support the use of Revatio in children but recognised the need for targeted ongoing surveillance in the form of postmarketing Phase IV studies in this relatively small group of patients to detect any rare or unexpected long term treatment emergent adverse events.

Recommendation

Because of the concerns raised, the evaluator could not recommend the extension of indication as requested by the sponsor. The evaluator recommended approval for children >7 years of age for all WHO functional classes for primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease. However, the evaluator recommended rejection for children <7 years of age due to the lack of demonstrable efficacy in this age group.

V. Pharmacovigilance Findings

Risk Management Plan

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

The sponsor indicated that no population specific risk was identified in the clinical paediatric program that would justify pharmacovigilance/risk management activities beyond those currently in place for the adult population.

Safety specification

Ongoing safety concerns as specified by the sponsor are shown in Table 16.

Table 16: Ongoing safety concerns

Identified risk	Nitrate interaction
Potential risks	Epistaxis/bleeding events Hypotension Non-arteritic anterior ischaemic optic neuropathy. (NAION) Medication errors associated with the use of the 50 ml vial Potential drug interactions: epoprostenol, bosentan, iloprost, ambrisentan
Missing or limited information	Paediatric population (prior to this submission) Long-term ocular safety Pregnancy Renal Impairment Cardiovascular safety Long-term mortality

The clinical evaluator reviewed the Safety Specification for clinical aspects but did not identify any safety findings in the clinical trials that were not included in the Safety Specification.

Proposed pharmacovigilance activities

The sponsor proposed enhanced pharmacovigilance (PhV) by way of a 'Data Capture Aid' (DCA) for the ongoing 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.¹¹

¹¹ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Collection and evaluation of safety data from clinical trials in the EU Paediatric Investigation Plan (PIP) are identified as additional PhV activities specific to this submission. Other proposed PhV activities included data from ongoing clinical studies, particularly that from Study A1481156.

Risk minimisation activities

The sponsor proposed routine risk minimisation strategies for all the important potential risks and missing information items.¹²

Summary

The OPR reviewer noted that the most serious risk of hypotension with Revatio relates to the concomitant administration of nitrates; therefore nitrates are contraindicated in the Revatio product label. The summary of the RMP was missing this identified risk in addition to the potential risk of hearing impairment/sudden hearing loss and risk minimisation for patients co-prescribed sildenafil with iloprost or bosentan. Routine risk minimisation strategies are proposed through the draft product information language.

It was recommended that the sponsor amend the RMP summary to:

- include the identified risk of nitrate interactions;
- include the potential risk of hearing impairment/sudden hearing loss;
- update the risk minimisation activities with the relevant draft Australian PI language;
- include the additional safety concerns of paediatric RTI/pyrexia, paediatric priapism and the potential drug interactions with iloprost or ambrisentan;
- include risk minimisation activities for “safety data is missing in PAH patients co-prescribed sildenafil with approved therapies iloprost or bosentan” ;and
- provide risk minimisation activities for missing data regarding co-prescription with ambrisentan.

It was also recommended that the sponsor provide critical comment on the observation that a number of the adverse events documented in the PI for sildenafil use in male erectile dysfunction (Viagra) are not listed in the Revatio draft PI. While this may be because the patient populations for each indication are quite different, it is also possible that due to the lower level of exposure in the PAH population, the likelihood of detecting such events is reduced.

The sponsor responded to the reviewer’s comments and the revised RMP was considered satisfactory.

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 compounding mixtures Ora-Sweet and Ora-Plus were of suitable quality, the resulting suspension is chemically and physically stable for at least 30 days at 2-8°C in natural HDPE bottles, the resulting suspension will remain sterile over this period (both Ora-Sweet and Ora-Plus contain preservatives to ensure anti-microbial quality) and a

¹² 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.

suitably accurate device will be used to dispense the suspension. In relation to bioavailability it was demonstrated that the 20 mg Revatio tablet is bioequivalent to the tablet crushed and mixed with apple sauce (both of these presentations were used in the clinical efficacy study). It was also shown that the proposed oral suspension was bioequivalent to the 20 mg tablet for AUC (90% CI 0.97-1.11) but slightly outside the accepted limit for C_{max} (90% CI 0.76-0.95) with no change in t_{max} . PSC also considered this submission and had no objections on pharmaceutical or biopharmaceutical grounds providing a number of matters were addressed by the sponsor. These issues were resolved with the TGA.

Nonclinical

The nonclinical evaluator had no objections to the registration of sildenafil for the proposed indication or for use with Ora-Sweet and Ora-Plus provided the clinical data adequately demonstrate safety of sildenafil in this age group, particularly for patients around 1 year of age. The data package did not contain any studies in juvenile animals which would have been useful as additional reassurance for the safety of sildenafil in this young age group. The available nonclinical data did not indicate any potential for new or exacerbated toxicity in paediatric patients. Exposure to sildenafil could be greater in infants around 1 year of age due to immature CYP3A4 activity and reduced clearance of sildenafil by the foetal form, CYP3A7. This could potentiate adverse effects in infants and require dosage adjustment.

Clinical

Clinical Evaluation

The clinical evaluator recommended approval for a reduced indication of children >7 years of age for all WHO functional classes for primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease. The evaluator recommended rejection for children 1-7 years of age due to a lack of efficacy in this age group (the data did not demonstrate a benefit in either functional or haemodynamic parameters in the treatment groups compared to placebo). The concerns noted by the evaluator included:

- Lack of efficacy in children 1-7 years of age
- No added efficacy benefit from higher doses of sildenafil compared to lower doses
- Lack of long term safety data for children
- Lack of data in children with WHO Functional Class IV (only 1 child).

Pharmacology

A palatability study was conducted in 4 adults who determined the optimal formulation was crushed Revatio tablets in a 75/25 blend of Ora-Sweet/Ora-Plus. A three arm bioequivalence study in 18 healthy adults demonstrated bioequivalence for the extemporaneous preparation proposed in the PI with the crushed tablet that was used in the clinical trial and the intact Revatio tablet for AUC but slightly out for C_{max} . A population pharmacokinetic analysis of the clinical study indicated that clearance plateaus at a body weight of 20-30 kg and weight was the main predictor of drug concentration for a particular dose. The analysis supported the dosing regimen of 10 mg for those <20 kg and 20 mg for those >20 kg so that the majority of children would have plasma concentrations of sildenafil within the therapeutic range.

Efficacy

Study A1481131

This was a multicentre, randomised (by weight), double blind, placebo controlled parallel trial of sildenafil (low, medium and high dose groups based on weight with doses ranging from 10-80 mg tds to achieve target plasma concentrations) vs placebo in 235 children aged 1-17 years with PAH (primary or secondary to transposition of the great arteries within first 30 days of life or surgical repair of congenital heart lesions within the preceding 26 months and no significant left sided heart disease and oxygen saturation $\geq 88\%$) for 16 weeks. The study had 90% power to detect a 15% treatment difference (protocol amendment, was originally 20%) which allowed for multiple comparisons between each dose and placebo. Patients were randomised to one of three dose groups or placebo by weight and their developmental ability to perform the primary outcome measure of a cardiopulmonary exercise test. Within those weight groups there were three different doses (low, medium or high), except for the lowest weight group. At baseline, 29% were in WHO Functional Class I, 53% in WHO Functional Class II and 17% in WHO Functional Class III. Only one patient had WHO Functional Class IV symptoms. Study completion was between 95-98% but just under half of each group were developmentally able to do the exercise test and analysed for the primary outcome measure.

The primary efficacy endpoint of percent change in pVO₂ at 16 weeks as measured by the child cycling on a stationary bike through a graded challenge indicated a dose dependent change which was of borderline significance (7.71%, 95% CI -0.19, 15.6, p=0.056). The absolute difference was 1.68 mL/kg/minute from a baseline of 17.61 mL/kg/minute. Within each dose group, the placebo subtracted differences in pVO₂ with 95% CI were: low dose=3.81% (-6.11, 13.73), medium dose=11.33% (1.71, 20.94) and high dose=7.98% (-1.64, 17.6). *Post hoc* subgroup analyses were performed but these were too small to draw conclusions. Analyses by type of PAH (primary vs secondary) indicated a trend to improved pVO₂ on sildenafil but the number of patients was too small to draw conclusions (PPH 14 vs -2% change on sildenafil combined vs placebo; secondary PAH 7.8 vs 1.9% change on sildenafil combined vs placebo).

Secondary measures included haemodynamic assessments and quality of life.

- Change in mPAP: Placebo subtracted change of -3.1 mmHg for sildenafil combined (95% CI -7.5, 1.3) compared with a baseline of 62.8 mmHg for sildenafil combined groups. Low dose change was +1.6 mmHg, medium dose change was -3.5 mmHg and high dose change was -7.3 mmHg.
- Change in WHO functional class: no change for patients in WHO Class I, for WHO classes II-IV there was an improvement in one class by 19% (low dose), 29% (medium dose) and 29% (high dose) vs 11% of the placebo group. A small percentage worsened by one class (3.4% of combined dose groups vs 6.7% of placebo patients). One patient improved by 2 classes.
- Change in time to pVO₂: Increases were seen in all sildenafil groups. 9.24% (95% CI -3.05, 21.54) increase in the sildenafil combined group compared to placebo.
- Change in Cardiac Index: Increases were seen in all sildenafil groups (combined sildenafil group vs placebo was 0.74 (95% CI 0.14, 1.34).
- Change in Pulmonary Vascular Resistance: Decreases were seen in the medium and high dose groups. Combined group change was -2.9 (95% CI -7.1, 1.3) Wood units.
- Change in Respiratory Exchange Ratio: Values ranged from 1.05 to 1.10 at Week 16, but some subjects did not reach maximal exercise.

- Change in Right Atrial Pressure: Small decreases were seen in all sildenafil groups (<1.5 mmHg).
- Change in Quality of Life: No difference in the child health questionnaire compared to placebo.

Study A1481131 Supplementary

A supplemental report to address the significant number of patients who were unable to complete the primary efficacy assessment for the above study was submitted. This analysis separated patients into those <7 years old (n=47), >7 years old and not developmentally able (n=42) and >7 years old and developmentally able. This had methodological problems being a small number of patients in a subset of the original study and examining secondary endpoints only. The results indicated that for those <7 years old, the haemodynamic results and quality of life results were similar to placebo but those >7 years old and non-developmentally able, the results were mixed.

Study A1481156

This is an ongoing long term open label extension study of 220 patients from the above efficacy study A1481131 with the 60 placebo patients re-randomised to sildenafil. At the time of this interim analysis, patients were exposed for >1 year (206 patients), >2 years (129 patients) and >3 years (88 patients). At 1 year, pVO₂ was numerically higher in all three dose groups but this was not significant (11% increase on low dose, 5% increase on medium dose and 2.6% increase on high dose). The assessment of WHO functional class maintenance or improvement was similar for all three dose groups at 1 year with 67-76% maintenance/improvement and at 3 years with 46-50% maintenance/improvement.

Safety

Safety data were derived from 234 patients from the main study and its extension with 206 exposed for 1 year and 88 exposed for ≥3 years. Adverse events were experienced by 100% of subjects with the most common being URTI (25%), headache (23%) and vomiting (23%) with a dose response seen for some events but this was not consistent. Discontinuations due to adverse events occurred in 12 subjects. Deaths occurred in 22 subjects but the evaluator deemed these not attributable to study medication (disease progression or complications). The Kaplan-Meier curves were similar for the dose groups but the numbers are small. Serious AEs occurred in 31% of patients with 6 events deemed related (including one death from the placebo to high dose group). Laboratory changes and vital signs of blood pressure and heart rate did not show significant change. Weight and height increased over time and no abnormal trends in cognitive development or motor development were seen although several patients had developmental disability. Five patients had worsening of colour vision (chromatopsia).

Risk Management Plan

The Office of Product Review accepted the RMP Version 5.2 for sildenafil. No changes were required.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

Adult studies in PAH use the 6 minute walk (6-MW) test as the primary efficacy measure but in children the administration of this test can be difficult especially for those who are very young. As an alternative measure agreed with the EMA, the sponsor used pVO₂ as a surrogate which was measured using a cardiopulmonary exercise test on a bicycle through

a graded challenge. The clinical evaluator accepted the use of pVO₂ for children >7 years of age but it should be noted that correlation of this surrogate with long term survival and quality of life has not been demonstrated. The main efficacy study showed a trend to improvement in pVO₂ which was of borderline significance however younger children and those with developmental difficulties could not be assessed for the primary endpoint (44% completion of primary endpoint, a significant deficiency). Secondary endpoints were generally supportive of efficacy but unable to demonstrate a significant effect. There was no apparent change in quality of life and no data on sildenafil's effect on morbidity or mortality. The change in WHO functional class favoured sildenafil compared to placebo. The study also was powered to detect a 15% improvement in pVO₂, however the result was only 3.81% for low dose, 11.33% for medium dose and 7.98% for high dose, indicating the study was under powered or the effect of sildenafil is less than expected. There was no 6-MW test as is usual for adults, however this could have been used in the older children or combined with a clinical endpoint. The long term extension study appeared to indicate maintenance of benefit in pVO₂ and WHO functional class but there did not appear to be a benefit from the high dose compared to the low dose.

Children 1-7 years of age

There was a lack of nonclinical data in juvenile animals and the nonclinical evaluator raised concerns about the use of sildenafil in infants due to immature CYP3A4 activity and reduced clearance of sildenafil leading to potentially greater safety concerns and dose adjustments. The lack of juvenile animal studies makes this assessment more difficult and therefore relies on the clinical data. The clinical evaluator had difficulties in assessing efficacy in this young age group due to an inability to successfully complete the test. The data that could be assessed using secondary efficacy endpoints only of haemodynamic parameters and quality of life did not demonstrate an improvement compared to placebo. The safety data appeared overall to be consistent with the adult data but there is a lack of long term safety data for this population and power to demonstrate an efficacy benefit. Therefore the data appear insufficient to support use in children 1-7 years of age at this time.

WHO functional classes I and IV

There was no improvement in WHO functional class for patients with baseline Class I therefore it is unclear whether this patient group should be included in the indication, given also the issues discussed above. There was also only one patient with WHO Functional Class IV in the primary efficacy study, therefore it is difficult to draw conclusions for this category but it may be impractical to cease treatment for a patient who was in Class III and has deteriorated to Class IV.

WHO Group I

The data submitted only comprised of patients with PPH and PAH secondary to congenital heart disease. WHO Group I includes other PAH categories, for example, persistent pulmonary hypertension of the newborn, for which the sponsor has not submitted any information. In keeping with other medicines for pulmonary hypertension, the indication should be modified to reflect these two groups.

Dose selection

It is not clear how the weight based dosing used in the main efficacy study (three dose groups based on three weight groups) relates to the doses proposed in the PI. This rationale should be explained by the sponsor. It appears that there is no added benefit from the high dose group compared to the low dose group, however there is some data to indicate the medium dose group may be better than the low dose group but these are not

significantly different. As with the adult data, there appears to be a lack of exercise related dose response.

Safety and RMP

The safety profile of sildenafil was considered by the clinical evaluator to be consistent with the adult data and the known safety profile of sildenafil. The evaluator did not identify any unexpected treatment emergent adverse events. Changes in vision were noted as has been reported in adults. Developmental data for cognitive and motor development were acceptable but there were a lack of data with respect to effects on endocrine/pubertal change.

Extemporaneous compounding

The PI provides for instructions to pharmacists to extemporaneously compound the oral suspension using 62 x 20 mg Revatio tablets mixed with Ora-Sweet (flavouring and sweetening agent) and Ora-Plus (suspending agent). Both Ora-Sweet and Ora-Plus are available in Australia but are not listed/registered on the ARTG and are commonly used by hospital pharmacies to prepare paediatric formulations. Information has been provided to demonstrate their quality and safety but a quantitative composition was not provided. A qualitative assessment of the excipients was undertaken by the nonclinical evaluator and found to be acceptable. Both products contain antimicrobial preservatives (potassium sorbate and methyl hydroxybenzoate) so that the suspension when made can be stored for up to 30 days at 2-8°C to enable a 30 day treatment for patients taking 10 mg tds (1 mL tds for patients <20 kg) or a 15 day course for patients taking 20 mg tds (2 mL tds for patients ≥20 kg). Extemporaneous compounding instructions in a PI is unusual and should only been used as an interim measure for specialised indications until a properly formulated product is available for registration. The sponsor stated that prior experience indicated an oral liquid of sildenafil would be difficult due to palatability and stability issues, therefore the best option would be a powder for oral suspension. However until this is developed, and given the unmet need for this serious disease in children, then an extemporaneous formulation is acceptable as an interim solution.

Pack size

It was noted that the suspension is made from using 62 x 20 mg Revatio tablets but the tablets are only supplied in packs of 90 tablets therefore there could be wastage of tablets. The suspension could also potentially be made from 12 x 100 mg Viagra tablets. The suspension should be made from Revatio tablets as the proposed indication is for Revatio only and not for Viagra and that this extemporaneously prepared suspension is an interim measure only until a powder for oral suspension is produced for registration in the future. This seems acceptable as an interim measure however if there is a delay then another pack size could be considered for registration.

Bioequivalence

The slight reduction in C_{max} for the bioequivalence of the proposed oral suspension and the registered tablet is unlikely to be clinically significant, given that the AUC was bioequivalent. T_{max} was unchanged and the variability of the oral suspension was not higher than that of the tablet.

List of Questions and sponsor response

The sponsor addressed some of the clinical evaluator's questions with the PK question to be addressed in the Pre-ACPM Response. In relation to children <7 years old, the sponsor indicated that additional data and analyses were submitted in Europe containing haemodynamic data to support this age group. They also advised that the FDA advisory

committee supported the use of haemodynamic data with PVRI being an appropriate surrogate endpoint. However, the data for PVRI in children <7 years old was not significantly different from placebo for any dose group. A similar finding was seen for change in mPAP and cardiac index.

Other data deficiencies

There was a lack of robust long term data on efficacy and safety, a lack of clinical outcome data on morbidity or mortality and methodological problems with the current data as discussed above. The data were also limited to two subgroups of WHO Group 1 PAH classification and limited for WHO Functional Class IV patients.

Summary

Overall the submission may be approvable for those patients 7-17 years old given the acceptable safety profile and trend for improvement from the efficacy data for a serious medical condition. The evidence for efficacy in patients <7 years old is not convincing and therefore not supported for registration due to a lack of primary endpoint assessment and failure of the secondary endpoints (including haemodynamics) to demonstrate a benefit in this age group. The data had some deficiencies and issues. Given PAH is a serious medical condition and that sildenafil is approved in adults for pulmonary arterial hypertension with WHO functional classes II-III, then ACPM's advice was requested on whether this is sufficient information to approve its use in children with primary pulmonary hypertension and PAH associated with congenital heart disease for all WHO functional classes. A modified indication is suggested based on the supplied data.

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

Treatment of paediatric patients aged 7-17 with primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease classified as WHO functional classes II-III.

The sponsor should address the following issues in the Pre-ACPM response:

- Was data collected and analysed to examine if there were any effects from sildenafil on endocrine/pubertal change?
- When will an oral suspension be ready for submission to the TGA for evaluation?
- Please explain how the final doses proposed in the PI were selected given the doses used in the main efficacy study.
- Please provide a table with the primary efficacy endpoint and key secondary endpoint results by baseline WHO functional classes.
- Please summarise the evidence to specifically support the inclusion of patients with WHO functional classes I and IV.

In addition, the Delegate directed the following questions to the ACPM:

- Should Revatio be approved for use in children 1-7 years of age?
- If Revatio is not recommended for use in children 1-7 years of age, then should the extemporaneous dosing instructions still be accepted?
- Should the indication include WHO functional classes I and IV for children 7-17 years of age with PPH and PAH associated with congenital heart disease?
- Should PPH be described differently given recent changes in the classification terminology which refer to idiopathic or heritable instead of primary?

Response from Sponsor

The sponsor submitted that Revatio is a valuable treatment option for children aged 1 to 17 years with PAH which is a life threatening disease. As exercise testing in young children has limited application, extrapolation to younger age groups is required using endpoints which can be assessed across all age groups.^{13,14} For this reason haemodynamic parameters were prospectively defined as important secondary endpoints in study A1481131.

The clinical efficacy of Revatio in children with PAH < 7 years of age, as measured by pulmonary haemodynamics, was addressed in detail during the EMA evaluation process and, as a result, the EMA issued a positive opinion with regard to the approvability of Revatio in children with PAH aged 1 to 17 years with the European Commission Decision adopted on 2 May 2011.

In the US, an FDA Advisory Committee was convened in July 2010 to discuss the treatment of paediatric PAH in general (including Revatio) and in particular what the appropriate study endpoint should be in paediatric PAH patients who are unable to perform exercise testing (children under 7 years of age). The FDA presented a meta-analysis of 13 PAH studies with different compounds and treatment classes in support of the FDA recommendation to use change in Pulmonary Vascular Resistance Index (PVRI) to assess effectiveness of adult approved drugs in paediatric PAH. The sponsor also presented a comparison of treatment effects of sildenafil on haemodynamic and exercise endpoints in adult and paediatric PAH (using the data from study A1481131). The Advisory Committee agreed that, for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the paediatric PAH population.¹⁴

In Study A1481131, patients under 7 years of age had lower mean baseline values for PVRI and mPAP and higher mean cardiac index (CI) than the older children. As normality assumptions were not met with the original analyses (initial submissions to TGA/EMA), further *post hoc* analyses were conducted on log transformed PVRI and CI data and provided as a result of the EMA questions. These analyses demonstrated that, despite the differences at baseline between the age groups, similar dose related proportional differences from placebo with PVRI and CI were found. Thus efficacy in children (as measured by pulmonary haemodynamics) under 7 years of age is convincing and similar to efficacy observed in children greater than 7 years of age.

In addition to the consistency observed with the <7 and ≥7 year-old subgroups, similar treatment effects were observed on haemodynamic endpoints in paediatric patients compared with those in adults in pivotal Study A1481140 (initial Revatio tablet marketing application). Due to the pathophysiological similarities of the disease in children across 1 to 17 years and in adults, there is no reason to expect differences in the clinical efficacy of sildenafil in children compared to adults or its efficacy in children in the age group of 1-7 years.

Long term safety data in the Interim A1481131/A1481156 CSR includes 1 year data for 206 subjects, 2 year data for 129 subjects and 3 year data for 88 subjects across all ages corresponding to 88.0%, 74.6% and 66.2% of those subjects who had the potential to reach 1, 2 and 3 years duration by the data cut on 15 May 2009, respectively. The safety

¹³ Paediatric addendum to the CHMP Guideline on clinical investigations of medicinal products for the treatment of PAH (CHMP/EWP/2213972/10).

¹⁴ FDA Advisory Committee meeting July 2010.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM225329.pdf>

profile from this long term data is consistent with that observed in the 16 week Study A1481131.

Left untreated, PAH is an aggressive debilitating disease ultimately resulting in death, regardless of age. With limited therapy options available in paediatrics, the sponsor believed that, along with the consistency observed in improvements in the exercise capacity and haemodynamic parameters in adults and in children, and a favourable safety profile including long term safety data with sildenafil across all age groups, these data support an indication for sildenafil for the treatment of PAH in children from 1 to 17 years.

The efficacy of sildenafil has been observed in PAH children of all ages. Thus, it would be inappropriate to deprive younger children, who are suffering from this life threatening disease with limited therapeutic options available, of the benefit they could derive from the use of Revatio.

The sponsor also addressed the questions posed by the Delegate.

Data on endocrine/pubertal change

No further juvenile toxicology studies in animals were conducted for the paediatric application and specific data on endocrine/pubertal change were not collected. The extensive package of toxicity studies conducted for inclusion in the original Revatio tablet submission included a pre- and post-natal development study in which sildenafil was administered to female rats from implantation to weaning at doses of 10, 30 or 60 mg/kg.

Exposure of offspring *in utero* and via milk during lactation had no effect on reproductive development (age at onset of vaginal patency and prepuceal fissure) or reproductive competency of adult offspring. Subchronic thorough carcinogenicity studies conducted with sildenafil utilized rats ranging from 6-7 weeks old at dose initiation showed no evidence of alterations in reproductive hormones. Therefore, there was no preclinical finding that would suggest potential detrimental effects of sildenafil on growth and maturation of the endocrine system in the intended paediatric population.

In Studies A1481131 and A1481156, the number of AEs reported in the *Reproductive System and Breast Disorders* System Organ Class (SOC) are low and do not suggest changes in endocrine/pubertal development with sildenafil.

Overall, the safety experience generated by the chronic use of sildenafil in paediatric PAH patients has not identified safety concerns with regard to endocrine/pubertal change.

Study A1481131 had no AEs in the *Endocrine Disorders* SOC reported with sildenafil. In A1481131 /A1481156 studies combined, two subjects who received sildenafil had an AE of hypothyroidism reported in *Endocrine Disorders*, both AEs were related to Down syndrome and not to sildenafil. One subject had an AE of blood parathyroid hormone increased reported, related to Down syndrome and not to sildenafil.

Preferred terms (PT) for the sildenafil associated AEs reported in *Reproductive System and Breast Disorders* included amenorrhea, dysmenorrhoea, endometriosis, erection increased, genital erythema, menorrhagia, menstruation irregular, metrorrhagia, priapism and spontaneous penile erection. Apart from the AEs erection increased, spontaneous penile erections and amenorrhoea (amenorrhoea was reported for 2 subjects in the sildenafil medium/medium treatment sequence), all other PT AEs were reported for no more than one subject in respective treatment groups.

The following AEs in *Reproductive System and Breast Disorders* were reported as treatment related: amenorrhea and endometriosis (1.3% each AE ([same subject]) in the high/high treatment sequence, erection increased (3.6% and 2.6% respectively in the sildenafil medium/medium and high/high sequences), genital erythema and priapism (each

reported in 1.3% in the sildenafil high/high treatment sequence) and spontaneous penile erections (5.5%, 1.3%, and 4.3% respectively in the sildenafil medium/medium, high/high and placebo/high treatment sequences). Apart from erection increased and spontaneous penile erections, there is no apparent dose response with sildenafil for reported AEs in this SOC.

Doses in PI

Population PK and PKPD models were used to evaluate the efficiency of various dosing regimens using a success criterion defined as an improvement in pVO₂ of at least 10% compared to baseline. The 10/20 mg dosage was identified as the optimal dose with respect to benefit and risk to treat children with PAH across the age range from 1-17 years.

For the purposes of the analysis a responder was defined as having a pVO₂ at Week 16 reaching a threshold of 10% improvement from baseline. Success rates for various doses across body weight were demonstrated for the fixed dose regimen with doses of 0, 10, 20, 30, 40 and 80 mg. The maximum response rate of ~48% at very high doses (40 mg and 80 mg tds) and the minimum response rate of 20% in placebo treated patients would be expected across the weight range (8 to 80 kg). The response rate for 20 mg in children >20 kg would decrease slightly to 42% across the weight range and therefore remains comparable to higher doses (> 85% of maximum response).

Likewise, the response rate for the 10 mg dose would achieve response rates in younger children (<20 kg) that would be also comparable to maximum doses (>80% of maximum response). The final dosage proposed corresponds to the medium dosage used in the main efficacy study, that is, 10 mg for body weight ≤20 kg and 20 mg for body weight between 20 and 45 kg. In patients above 45 kg, the proposed dose of 20 mg corresponds to an interpolation between the low dose (10 mg) and the medium dose (40 mg). As noted in the sponsor's *Clinical Study Report*, the medium dose group demonstrated clinically relevant effects on pVO₂ and with the high dose group no further benefit was observed. Therefore 10 mg tds for weight ≤ 20 kg and 20 mg tds for weight > 20 kg would achieve close to the maximum achievable responder fraction across all weights.

Furthermore, 10 mg tds for weight ≤ 20 kg and 20 mg tds for weight > 20 kg achieved similar exposure and similar treatment effects (exercise capacity and haemodynamics) compared to adults treated with 20 mg tds (Study A1481140).

Importantly, with the 10/20 mg dosage, the upper limit of the 90% prediction interval for C_{av,ss} is less than 4 fold greater than the efficacious exposure (EC₉₀). Whereas, higher dosages would expose children to considerably higher exposures; for example, with 20/40 mg, the upper limit is more than 8 fold greater than EC₉₀.

In summary, the 10/20 mg dose demonstrated clinically relevant effects on pVO₂ and/or pulmonary haemodynamics; the response rates were comparable to those achieved with higher doses; exposures achieved with the 10/20 mg dose are similar to those in adults and do not exceed 4 times the efficacious exposure.

In conclusion, based on all these considerations, 10 mg tds for weight ≤ 20 kg and 20 mg tds for weight > 20 kg was recommended.

As requested in the clinical evaluation report, the sponsor provided a table which summarised the fraction of subjects below the EC₉₀ (31.19 ng/mL) or EC₅₀ (23.7 ng/mL), across the weight groups by simulation. There was only a small portion of patients, that is, around 18% to 30% at a weight range from 17 to 20 kg which may have an exposure below EC₅₀. More importantly, the proposed dose regimen is targeting the adult exposure

at the clinical dose of 20 mg tds and in line with the medium dose used in the main paediatric efficacy study.

Efficacy endpoints by WHO functional classes

The sponsor provided a table which presented the pVO₂, PVRI, mPAP and CI results by baseline WHO functional class. Whilst the small number of subjects in each dose group makes interpreting the efficacy data by dose for baseline functional class difficult, the results are generally consistent with the medium and high doses displaying improvements over placebo across all baseline functional classes, including Class I and IV. These analyses of PVRI and CI used a consistent method of estimation of oxygen consumption, where cardiac output was assessed by Fick method and a log transformation of the data. These data were generated in response to questions from the EMA during evaluation and are reflected in the agreed EU Summary of Product Characteristics.

Evidence for WHO functional classes I and IV

The non-specificity and the subtle presentation of PAH symptoms present difficulties in establishing a diagnosis both in adults and children.¹⁵ Children are not always reliable in reporting symptoms, thus PAH is often not diagnosed until after an upper respiratory tract infection. Children tend to be diagnosed prior to the development of right heart failure and therefore have less advanced functional class at diagnosis, although their haemodynamics can be as severely compromised as in adults.^{16,17}

The assessment of WHO functional class for patients with pulmonary hypertension remains widely used in adult PAH patients to evaluate functional impairment.¹⁸ It can also be useful in older children, but less so in infants or young children. WHO functional class may also be inadequate to characterise a child with preserved cardiac output and no, or limited, functional impairment at rest, but with syncope upon over exertion or with even mild exercise. The consensus among opinion leaders is that under such circumstances treatment should be initiated.¹⁹

Standardised guidelines are needed for the physicians taking care of paediatric pulmonary hypertension so that WHO functional class is used reproducibly in children.

Although pathophysiological changes in PAH are similar in children and adults, the natural history of PAH can differ.^{16,18} The presenting symptoms of PAH are usually severe in children and the rate of disease progression is usually faster.¹⁸ Therefore, early and sometimes aggressive therapy may be required in younger children.¹⁸ Barst et al compared demographics, clinical course and management of 99 patients with childhood onset idiopathic PAH (chIPAH, age at diagnosis ≤18 years) and 1295 patients with adult onset IPAH (adIPAH, age at diagnosis ≥19 years).¹⁶ AdIPAH was associated with worse functional class at diagnosis compared with chIPAH.

AdIPAH was also associated with worse haemodynamics indicative of impaired right ventricular function at PAH diagnosis compared with chIPAH: mean right atrial pressure

¹⁵ Haworth SG. The management of pulmonary hypertension in children. *Arch Dis Child* 2008; 93: 620–625.

¹⁶ Barst RJ, Ivy D, Badesch DB et al. REVEAL Registry: Comparison of patients with childhood-onset and adult-onset idiopathic pulmonary arterial hypertension. *J Heart Lung Transplantation* 2009; 28: S146.

¹⁷ Barst RJ, Ivy D, Badesch DB, et al. REVEAL registry: comparison of patients with childhood-onset and adult onset pulmonary vascular disease associated with congenital heart disease. *J Heart Lung Transplant* 2009; 28: S312.

¹⁸ Haworth SG, Beghetti M. Assessment of endpoints in the pediatric population: congenital heart disease and idiopathic pulmonary arterial hypertension. *Curr Opin Pulm Med*. 2010; 16: S35-41.

¹⁹ Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. *Eur Respir J* 2011; 37: 665–677.

(mRAP) 10.2 mmHg vs 6.6 mmHg, respectively ($p < 0.001$); and CI 2.2 l/min/m² vs 3.6 l/min/m², respectively ($p < 0.001$) while mPAP and PVRI were similarly elevated.^{16,20} These differences help explain the limited utility of WHO functional class assessments that measure limitation in daily living activities that are more appropriate for adults than children. Thus functional class (FC) needs to be interpreted with caution in children and is not directly aligned with FC in adults.

The sponsor presented a table which showed the baseline characteristics for the adult (A1481140) and paediatric (A1481131) studies with sildenafil. The majority of paediatric subjects (A1481131) were FC I or II at baseline, whereas the majority of adult subjects (A1481140) were FC II or III at baseline. Despite these differences in baseline FC, similarities in baseline haemodynamic parameters in these studies indicate that the paediatric and adult study populations were comparable and thus should have the opportunity to receive benefit from treatment.

Despite these limitations with WHO FC for a paediatric PAH population, the results were generally consistent with the primary and secondary endpoints across baseline functional classes.

In addition, although the baseline functional class characteristics may suggest that there is little room for improvement for functional class in Study A1481131, a dose response with changes in functional class was observed. A similar effect with regard to functional class was observed in Study A1481140.

The extrapolation of the definition and classification of PAH from adult patients to children is not always straightforward, especially for very young children. As with adults, children can be difficult to diagnose but additional challenges arise in the assessment of disease severity due to the inability of young children to perform exercise tests reliably or reproducibly, and the difficulty in using WHO FC in young children.

In conclusion given the limitations of assessing WHO FC in paediatrics the sponsor did not believe WHO FC assignment at diagnosis is appropriate to be the basis for withholding Revatio treatment from children especially as improvements were noted in haemodynamics in subjects of WHO FC I, II or III/IV at baseline.

The sponsor also pointed out that study A1481131 was powered with respect to the comparison of the sildenafil dose groups combined (average across 3 groups) and placebo, and not "multiple comparisons between each dose and placebo", as noted by the Delegate.

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, recommended approval of the submission for a major variation to change the patient population and an extension of indications to include:

Treatment of paediatric patients aged 1 – 17 years with idiopathic and heritable pulmonary hypertension and pulmonary hypertension associated with congenital heart disease classified as WHO functional classes II-IV.

In making this recommendation, the ACPM considered the acceptable safety profile and trend for improvement from the efficacy data for a serious medical condition was acceptable in support of the application in the age range 7 to 17 years.

²⁰ Badesch D, Raskob GE, Elliott CG et al. Pulmonary arterial hypertension: Baseline characteristics from the REVEAL Registry. *Chest* 2010; 137: 376-387.

The ACPM agreed with the Delegate that the lack of primary endpoint assessment and failure of the secondary endpoints (including haemodynamics) did not provide sufficient evidence for efficacy in patients younger than 7 years old. Although testing for improvement in cardio-pulmonary exercise capability in the very young would always be a challenge, the choice of an exercise test that involved advanced coordination thwarted any possibility of assessment in this age group. Nonetheless, there is no theoretical reason why the product would be less efficacious in the 1- 7 years age group and the committee was of the view that there was sufficient safety data to support a recommendation in this age group.

No evidence of efficacy and safety in patients in WHO Class I patients was provided to support this aspect of the application. However, despite the limited data in support of treatment in WHO Class IV patients the committee was of the view that it would not be possible to withdraw treatment at this stage.

The ACPM also recommended changes to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Outcome

The sponsor withdrew the application before a decision was made.

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Reference/Publication #