2 April 2012
EMA/111056/2012
Human Medicines Development and Evaluation

Revatio-000638-Article 45/020: EPAR – Assessment Report

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Revatio
INN (or common name) of the active substance(s):	sildenafil
MAH:	Pfizer
Currently approved Indication(s)	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. *Revatio solution for injection is for the continued treatment of patients with pulmonary arterial hypertension classified as WHO functional class III who are currently prescribed oral Revatio and who are temporarily unable to take oral medication* (indication not yet approved)
Pharmaco-therapeutic group (ATC Code):	G04B E03
Pharmaceutical form(s) and strength(s):	Tablets 20 mg
Rapporteur:	**Name Pieter de Graeff** Tel: Email:

1. INTRODUCTION

On 12 December 2008, the MAH submitted 2 paediatric studies to document use of intravenous Revatio in children, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. The applicant did not propose any claims based on this submitted study. At the time of submission no medicinal product was approved for PAH for use in a paediatric population, though bosentan SPC contained some paediatric PK data in section 4.2 to guide dosing. Revatio IV was also not registered for adults at that time.

2. SCIENTIFIC DISCUSSION

2.1. Clinical aspects

The MAH submitted reports for:

- A1481134; a randomized, multicenter, double-blind, placebo-controlle, dose-ranging, parallel group study of intravenous sildenafil in the treatment of children, aged 0-17 with pulmonary hypertension after corrective cardiac surgery.
- A1481157; a 7-day, open-label, multicenter, pharmacokinetic study (part 1) followed by a 7-day, randomized, multicenter, double-blind, placebo-controlled, dose-ranging, parallel group study (part 2) of IV sildenafil in the treatment of neonates with persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure and at risk for PPHN.

Clinical study(ies)

A randomised, multicenter, double-blind, placebo-controlled, dose ranging, parallel group study of intravenous sildenafil in the treatment of children, aged 0 to 17 with pulmonary hypertension after corrective cardiac surgery, A1481134.

Methods

- Objective(s)

Primary:

To assess the efficacy of intravenous (IV) sildenafil, over 24 hours of treatment, on pulmonary hypertension during the post-operative period in children aged 0 (☐34 weeks gestational age) to 17 years with congenital heart disease who have undergone corrective cardiac surgery.

Secondary:

To assess the safety and tolerability of IV sildenafil in children with corrected congenital heart disease with pulmonary hypertension,

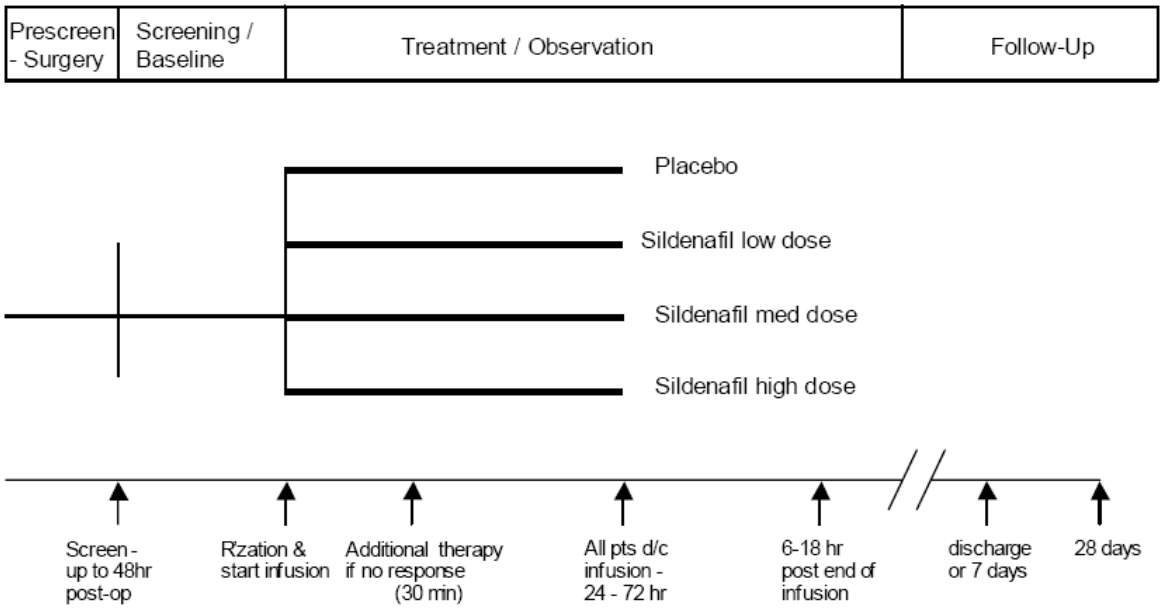
To establish an effective dose range of IV sildenafil in the treatment of pulmonary hypertension in children following corrective cardiac surgery

To investigate the pharmacokinetic (PK)-effect relationship, to determine the population PK parameters and

To evaluate the healthcare resource utilisation associated with the use of sildenafil compared to alternate therapies.

- Study design

Randomisation of subjects was to be stratified by age (neonate or non-neonate) and by study centre. They were to be randomized 63 patients per group, however only 18 patients were randomized.



- Study population /Sample size

Eighteen male or female subjects aged 0 (>34 weeks gestational age) to 17 years (up to one day before 18th birthday). Subjects undergoing corrective cardiac surgery (2 ventricle repair), for at least one of the lesions or procedures specified in the protocol and subjects who had a clinical diagnosis of post-operative pulmonary hypertension and a systolic pulmonary artery pressure >50% of the systolic arterial blood pressure (>75% for neonates □28 days) confirmed by qualifying Doppler echocardiogram or pulmonary artery (PA) catheter.

- Treatments

Three intravenous sildenafil dosage regimens were selected to achieve target sildenafil plasma concentrations of approximately 40, 120, and 360 ng/mL, respectively, for the three dosage regimens. Each regimen consisted of a bolus loading dose infused over five minutes, followed by a maintenance infusion for 24 to 72 hours, the infusion of study drug continued for a minimum of 24 and maximum of 72 hours.

- Outcomes/endpoints

The efficacy evaluations included: receipt of additional therapy for the treatment of post-operative complication of pulmonary hypertension within 24 hours of the start of study drug infusion. Time to first extubation, length of hospital stay, length of stay in intensive care unit, total duration of administration of additional therapy for pulmonary hypertension and deaths assessed up to 28-day follow-up. Change from baseline in post-operative inotrope scores, change from baseline in serum lactate levels (as a surrogate for cardiac output evaluation) and change from baseline in haemodynamic parameters at post-baseline assessment times. Plasma concentration data for sildenafil and its metabolite (UK-103,320) was obtained from all subjects in this study.

- Statistical Methods

As the study was terminated early, the statistical analysis plan was amended prior to unblinding the study and the efficacy data were listed. The applicant did a post-hoc analysis.

Results

- Recruitment/ Number analysed

This study was stopped due to low enrolment because of the rarity of clinically significant post-operative pulmonary hypertension associated with current treatment practices.

No of Subjects	Placebo	Sildenafil		
		IV Low	IV Medium	IV High
Randomised	5	4	5[a]	4
Treated	5	4	4	4
Completed	4	4	3	4
Discontinued	0	0	2	0
Died	1[b]	0	0	0
Analysed for Adverse events	5	4	4	4
Analysed for Laboratory data	5	4	4	4

18 subjects were randomised but only 17 were treated
[a]Subject 10210004 was randomised but not treated
[b]Subject 10070001died during follow-up

- Baseline data

	Placebo		Sildenafil IV					
			Low		Medium		High	
	Male	Female	Male	Female	Male	Female	Male	Female
Number of subjects	4	1	2	2	2	2	1	3
Age								
>1 month-2 years	3	1	2	1	2	2	1	3
>2 years-12 years	0	0	0	1	0	0	0	0
>12 years-18 years	1	0	0	0	0	0	0	0
Mean Weight (kg)	18.4	3.9	6.3	9.7	5.7	8.2	5.2	5.2
Mean Height (cm)	78.1	49.0	62.0	111.8	56.0	70.8	59.5	65.3

Age ranged (months) 3-178 and 5-5 in the placebo group; 3-178 and 3-4 in the low sildenafil group; 3-77 and 3-77 in the medium sildenafil group; and 3-11 and 6-25 in the high sildenafil group, respectively for group and gender.

- Efficacy results

Endpoint	Placebo (n=5)	Sildenafil (n=4)	Sildenafil (n=4)	Sildenafil (n=4)
Primary		IV Low	IV Medium	IV High
Additional therapy within 24hrs of start of study drug	2 (Cisatracurium; NO)	1 (NO)	1 (NO)	0
Secondary				
Time to first extubation (days)	4 to 11	-1 to 5	1 to 3	1 to 11
Time to first discharge from hospital	11 to 21	4 to 20	4 to 27	6 to 35
Time to first discharge from intensive care unit	5 to 15	1 to 8	2 to 7	2 to 12

Four of the seventeen treated subjects, two each on sildenafil (17%) and placebo (40%), received additional therapy for treatment of post-operative pulmonary hypertension within 24 hours of start of study drug infusion. Eight of the seventeen treated subjects; five (42%) on sildenafil and three (60%) on placebo, received additional therapy to Day 28 follow-up. The duration of therapy ranged from 6 to 601 hours.

No PK/PD results have been reported.

- Safety results

Type of Adverse Event	Total	Placebo (n=5)	Sildenafil (n=4)	Sildenafil (n=4)	Sildenafil (n=4)
			IV Low	IV Medium	IV High
AEs	45				
Treatment related AE	0	0	0	0	0
Severe AE	6	3	2	0	1
Death	4*	2	0	0	0
Discontinued due to AE	1**	0	0	0	1**

*2 deaths before randomization, 2 other deaths not related to study treatment

** temporarily

There were six subjects with severe adverse events. The two placebo subjects reported severe superior vena caval occlusion due to the disease under study, and severe pneumonia, respectively. A subject on sildenafil IV high reported severe anuria and severe pulmonary hypertension due to the disease under study. The two subjects on on sildenafil IV low reported a severe apnoeic attack due to possible gastroesophageal reflux, and severe haemorrhage due to surgery, respectively.

CHMP comments :

The used endpoints in the submitted studies are not validated and focus on short term management. If any conclusion on primary endpoint and secondary endpoints can be drawn, these should be handled with care due to the small number of patients. A conclusion on the benefit risk ratio is difficult to draw. No dose advice can be drawn based on the presented data. Furthermore, the patient group except for two, is limited to patients <2 years. As long as the applicant does not make any dose recommendations or proposes claims, a specific conclusion is difficult to draw. Therefore, a definite benefit risk evaluation for a specific dose-advice cannot be made.

A 7-day, open-label, multicenter, pharmacokinetic study (part 1) followed by a 7-day, randomized, multicenter, double-blind, placebo controlled, dose-ranging, parallel group study (part 2) of iv sildenafil in the treatment of neonates with persistent pulmonary hypertension of the newborn (pphn) or hypoxic respiratory failure and at risk for PPHN, A1481157

Methods

- Objective(s)

The primary objective for Part 1 of this study was to evaluate the pharmacokinetics of intravenous (IV) sildenafil in near term and term newborns with PPHN or with hypoxic respiratory failure and at risk for PPHN.

The secondary objectives for Part 1 of the study were: to assess the safety and tolerability of IV sildenafil, and to characterise the pharmacokinetics of sildenafil in newborns with PPHN or hypoxic respiratory failure and at risk of developing PPHN.

- Study design

The study comprised three phases; a screening phase up to 72 hours of age, a treatment phase during which subjects received study drug for at least 48 hours and for up to seven days [168 hours (inclusive of times off study drug infusion)] with or without the addition of standard treatment, and a follow-up phase which consisted of two visits; one conducted at seven ± three days after the final termination of study treatment or at the time of hospital discharge, whichever came first, and the other on Day 28 ± three days. For the purpose of this study, standard treatment was inhaled nitric oxide (iNO) and/or extracorporeal membrane oxygen (ECMO).

- Study population /Sample size

Male or female subjects, ≤ 72 hours of age and ≥ 34 weeks gestational age, with PPHN or hypoxic respiratory failure associated with: idiopathic PPHN, meconium aspiration syndrome, respiratory distress syndrome, sepsis, and/or pneumonia. They also had to have an OI ≥ 15 on two separate occasions, calculated using arterial blood gas taken at least 30 minutes apart.

- Treatments

The loading dose infusion was extended to 30 minutes. For subjects in Group 7, no loading dose was administered and for subjects in Group 8 the duration of the loading dose was extended to 3 hours (180 minutes). Following the loading dose infusion, a maintenance dose infusion was administered at a constant infusion rate. This continued for at least 48 hours, and for up to seven days

The dose for the first treatment group was targeted to produce a plasma concentration of approximately 40ng/ml. Doses were escalated for subsequent treatment groups.

- Outcomes/endpoints

Blood samples for pharmacokinetic assay were collected at: 5 and 30 minutes after the end of the loading dose infusion, every 24 hours from the start of the study drug infusion, just prior to the end of the study drug infusion and at 1, 4, 8, 12, 24, 48, and 72 hours after the end of the study drug infusion.

In Group 7, blood samples for pharmacokinetic assay were collected at 6 and 12 hours after the start of study drug infusion As the duration of the loading dose in Group 8 was 3 hours, blood samples for pharmacokinetic assay were collected at 30 minutes after the start of study drug infusion and just before the loading dose was completed.

- Statistical Methods

No hypothesis testing was performed. The population pharmacokinetic analysis was performed using the Nonlinear Mixed Effects Modelling software.

Mixed-effects pharmacokinetic models were used to simultaneously describe the natural log-transformed plasma concentration-time data for sildenafil and UK-103,320. Since biotransformation to UK-103,320 is the primary route of elimination of sildenafil in adults, it was assumed for purposes of model development, that sildenafil was completely metabolised to UK-103,320 in neonates. One- and two-compartmental pharmacokinetic models, parameterised in terms of sildenafil clearance (Clpar), central volume of distribution of sildenafil (V1par), inter-compartmental clearance of sildenafil (Qpar), peripheral volume of distribution of sildenafil (V2par), UK-103,320 clearance (Clmet), central volume of distribution of UK-103,320 (V1met), inter-compartmental clearance of UK-103,320 (Qmet), and peripheral volume of distribution of UK-103,320 (V2met) were evaluated, in order to select a base pharmacokinetic model. Covariates such as body weight, age, gender, and concomitant administration of other CYP3A4 substrates were included in the base model to form the full model. The Wald's approximation method procedure was applied to the full model to identify the final covariate model. Model selection and covariate inclusion was based on the change in the minimum objective function value, evaluation of model diagnostic plots, and clinical significance of the covariate effect.

Results

- Recruitment/ Number analysed

Only Part 1 has been conducted, because the study was terminated prematurely.

	Sildenafil
Screened	36
Assigned to study treatment	
Treated	36
Completed	31
Discontinued	5
Analysed for safety	
Adverse events	36
Laboratory data*	33
Safety population	36

* For three subjects (10030002, 10110017 and 10110031) there were no post-screening, on-treatment laboratory measurements recorded.

- Baseline data

	Sildenafil		
	Male	Female	Total
Number of subjects	17	19	36
Age (hours)*	35.5 (12 – 71)	33.2 (11 – 70)	34.3 (11 – 71)
Gestational age (weeks)	39.0 (36.0 – 41.0)	39.5 (37.0 – 42.0)	39.3 (36.0 – 42.0)
Race: W/B/A/H/O	5/4/2/4/2	5/7/1/4/2	10/11/3/8/4
Weight (kg)	3.6 (2.9 – 4.4)	3.3 (2.5 – 4.2)	3.4 (2.5 – 4.4)
Length (cm)	49.6 (34.5 – 54.5)	50.2 (46.5 – 53.5)	49.9 (34.5 – 54.5)

Primary Diagnosis	Associated Disease	Sildenafil N=36
Hypoxic respiratory failure	Pneumonia Respiratory distress syndrome	1 3
Idiopathic PPHN	Not Applicable	2
PPHN	Sepsis Pneumonia Respiratory distress syndrome Meconium aspiration syndrome	4 1 5 20

- Efficacy results

One- and two-compartmental pharmacokinetic models, parameterised according to sildenafil and it's metabolite UK-103,320.

PK Parameter	Abbreviation	Mean	SD
Clearance of sildenafil	Clpar (for 3.5 day old)	1.720 l/hr	0.192
Central volume of distribution of sildenafil	V1par	10.40 l	0.964
Inter-compartmental clearance of sildenafil	Qpar	0.188 l/hr	0.053
Peripheral volume of distribution of sildenafil	V2par	12.00 l	5.190
Clearance UK-103,320	Clmet	3.800 l/hr	0.466
Central volume of distribution of UK-103,320	V1met	7.560 l	3.360
Inter-compartmental clearance of UK- 103,320	Qmet	3.260 l/hr	0.888
Peripheral volume of distribution of UK-103,320	V2met	25.90	6.950

- Safety results

Number of subjects with:	All Causality	Treatment Related
Treatment emergent adverse events	20	5
Death	1	0
Serious adverse events	4	0
Severe adverse events	5	0
Discontinued due to treatment emergent adverse events	4	2
Number of adverse events	41	5

One subject died during the study. This child died from a combination of her underlying illnesses of meconium aspiration, birth asphyxia and pulmonary hypertension which was further complicated by tension pneumothorax. Four subjects reported treatment emergent serious adverse events; one had hypotension, one had anomalous pulmonary venous connection, and two had a pneumothorax. None of these events were considered to be treatment related.

Four subjects discontinued study treatment due to treatment emergent adverse events; one due to hypotension, two due to labile blood pressure, and one due to anomalous pulmonary venous connection, also reported as a serious adverse event. One case of labile blood pressure and the hypotension were considered to be caused by the study drug.

The conclusion drawn by applicant on this study were:

CHMP comments:

The relatively long duration of a sildenafil infusion started soon after birth, allowed characterisation of the maturation of sildenafil clearance in neonates during the early post-natal period, and was consistent with previous reports of the rapid maturation of CYP3A4 during this period of life.

Sildenafil pharmacokinetics in neonates with PPHN was characterised by high inter-individual variability and moderately high residual variability. The inability to detect significant covariates, other than age, may be related to the small number of subjects in the study and the high variability. Therefore, other covariate effects on sildenafil and UK-103,320 pharmacokinetics could not be ruled out.

Sildenafil clearance in neonates at 10 days of age was predicted to be similar to that in adults after adjustment for body weight. Routine dose adjustment to account for the expected decrease in concentrations during a continuous sildenafil infusion may not be necessary, given the expected margin of safety and tolerability of sildenafil and the high inter-individual variability in sildenafil pharmacokinetics. An increase in dose during the infusion may be considered if warranted by the subject's clinical response. High inter-individual variability was observed in the pharmacokinetics of sildenafil and UK-103,320 in neonates.

Inter-individual variability in the pharmacokinetics of sedative drugs used commonly in similar neonatal populations in intensive care settings have been reported to be high, and may be partly related to the variable disease states of the critically ill neonates. Although sildenafil doses may be initiated in neonates with PPHN using the mean pharmacokinetic parameters reported in this study, some titration of sildenafil dose to clinical response may be necessary, given the high inter-individual variability in pharmacokinetics, as well as the lack of information on sildenafil efficacy in this population. The pharmacokinetic parameters determined in full term neonates with PPHN in this study may not be representative of those in healthy neonates or pre-term neonates.

Conclusions

The conclusions of the submitted study and the use of the modeling should be interpreted with care due to the small number of subjects and the unknown development of the metabolic system responsible for the metabolism of sildenafil in this group of patients. That the clearance of sildenafil in patients 10 days of ages can be used for extrapolation to adults after adjustment of body weight may be coincidence and should be intrepreted with utmost care. This type of modeling may not be very useful in predicting the pharmacokinetics in children without incorporating the most important covariate as the maturation, the metabolic systems responsible for the elimination of sildenafil.

Applicant did not make an attempt to use adult data for extrapolation to the group of children of different age.

3. Overall conclusion and recommendation

Overall conclusion

The applicant did not propose any claims based on this submitted study A1481134.The used endpoints in the submitted studies are not validated. A conclusion on the benefit risk ratio is difficult to draw. No dose advice can be drawn based on the presented data. Furthermore, the patient group is limited to patients <2 years. As long as the applicant does not make any dose recommendations or proposes claims, a specific conclusion is difficult to draw for the assessor. Therefore, a definite benefit risk evaluation for a specific dose-advice cannot be made. For study A1481157, the conclusions of the submitted study should be interpreted with care mainly due to the small number of subjects.

In summary, information is submitted on the use of intravenous sildenafil in children but no further conclusion can be made due to the limited number of patients, the lack of any claim, in particular on dosing and the fact that Revatio IV itself was not registered for adults at the time of submission. As long as the applicant does not make any claims, there is no need for a further assessment.

Recommendation

No further action required.