21 February 2013
EMA/161379/2013
Committee for Medicinal Products for Human Use (CHMP)

Revatio

(Sildenafil)

Procedure No. EMEA/H/C/000638/A46/0040

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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(s):	Revatio 20 mg film-coated tablets Revatio 0.8 mg/ml solution for injection Revatio 10 mg/ml powder for oral suspension
INN (or common name) of the active substance(s):	Sildenafil (as citrate)
MAH (s):	Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom.
Pharmaco-therapeutic group (ATC Code):	G04BE03
Pharmaceutical form(s) and strength(s):	Film-coated tablet.
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EXECUTIVE SUMMARY

This is an assessment of data pertaining to Revatio (sildenafil) in accordance with Article 46 of Regulation (EC) No 1901/2006. The Market Authorisation Holder (MAH) is submitting a clinical study report (CSR) **A1481276**, a single-arm study to investigate safety and efficacy of sildenafil in near-term and term newborns with Persistent Pulmonary Hypertension of the Newborn (PPHN).

This study was discontinued after enrolling only 4 patients (due to recruitment difficulties). The MAH does not consider that the results influence the benefit/risk of Revatio, and does not propose any labeling changes.

I. INTRODUCTION

REVATIO (sildenafil citrate) was approved for the treatment of PAH through the centralised procedure in 2005. In the adult population, the approved dosage regimen is one 20-mg tablet administered 3 times daily (TID).
Revatio was approved in Europe in May 2011 for paediatric PAH (EMEA/H/C/638/II/028). In paediatric patients (1 year to 17 years), the recommended dose in patients ≤ 20 kg is 10 mg TID and for patients > 20 kg is 20 mg TID. Higher than recommended doses should not be used in paediatric patients with PAH.
Pfizer updated the SmPC in Europe in September 2011 to include mortality data from the long-term extension study A1481156, to reinforce the dosing recommendations for this population, and to introduce a warning that higher than recommended doses should not be used in paediatric patients with PAH.

Sildenafil for the treatment of PAH is available orally as film-coated tablets containing sildenafil citrate equivalent to 20 mg of sildenafil and a 10 mg/mL powder for oral suspension (approved in the EU in March 2012).
The intravenous formulation is available as a solution for injection, 0.8 mg of sildenafil per ml of solution.
The recommended dose for the treatment of PAH is 10 mg (corresponding to 12.5 ml) three times a day administered as an intravenous bolus injection.

II. SCIENTIFIC DISCUSSION

Clinical Studies in Paediatric Pulmonary Hypertension of the Newborn

A brief descriptions of these studies are presented in Table 1.

Table 1. Summary of Studies Conducted in Patients with Persistent Pulmonary Hypertension of the Newborn

Study Number	Design	Dosing Regime	Sample Size	Status
A1481157	A 7-day, open-label, multi-centre, pharmacokinetic study (part 1) followed by a 7-day, randomised, multicentre, double-blind, placebo-controlled, dose-ranging study in newborns with PPHN or hypoxic respiratory failure and at risk for PPHN	IV dosing targeting exposure of 40 to 360 ng/mL	Target 20-25 part 1, 256 part 2 Enrolled 36	Completed[a]
A1481276	A single-arm, single centre study to investigate safety and efficacy of sildenafil in near-term and term newborns with PPHN	IV sildenafil loading dose of 0.1 mg/kg over 30 minutes, followed by maintenance dose of 0.0 mg/kg/h for up to 14 days.	Target 40 Enrolled 4	Premature halt in June 2012 for feasibility reasons
A1481283	A follow-up investigation for patients completing study A1481276 to investigate developmental progress 12 and 24 months following completion of sildenafil treatment	None	Target 40 To enroll 1	Planned LSLV November 2013
A1481316	A multi-centre, randomized, placebo-controlled, double-blind, two-arm, parallel group study to evaluate efficacy and safety of IV sildenafil in the treatment of neonates with PPHN or hypoxic respiratory failure and at risk for PPHN, with a long term follow-up investigation of developmental progress 12 and 24 months after completion of study treatment	IV sildenafil, loading dose of 0.1 mg/kg over 30 minutes, followed by maintenance dose of 0.03 mg/kg/h for up to 14 days	64 (32 for each arm)	Planned FSFV December 2012

a. Study terminated due to difficulty with enrollment.
Abbreviations: FSFV=first subject first visit; PPHN=Persistent pulmonary hypertension of the newborn.

Study A1481276, which is the subject of the report, is a study in paediatric patients diagnosed with PPHN that was originally included in the Paediatric Investigation Plan (PIP) decision P/244/2009 dated 2 December 2009. The study was halted prematurely after recruitment of 4 patients in June 2012 with agreement from the EMA Paediatric Committee (PDCO), as there had been poor enrollment and it was discontinued for feasibility reasons. The extension study A1481283 is ongoing to ensure follow up of one eligible patient from Study 1481276.

The PIP for Revatio has now been modified to remove study A1481276 and includes an alternative PPHN study (Study A1481316) at the request of PDCO, and this is included in the PDCO decision P/0158/2012, dated 25 July 2012. The PIP now includes 2 studies in PPHN, namely, A1481157, which has completed, and Study A1481316, which is due to start in 4Q 2012/1Q 2013.

All PPHN studies employed the IV solution for injection, being a suitable formulation for use in these patients. The variation application consisting of the full relevant data package (containing all the PPHN studies, ie, studies A1481157, A1481276, A1481283 and A1481316) is expected to be submitted.

Clinical Studies in Paediatric PAH

These include studies: A1481131, -56 and -34, which formed the basis of the paediatric indication granted in 2011 and are not discussed further in this report. Study A1481298 for paediatric patients with PAH, has just started in Japan, though no patients have been recruited.

II.1 Information on the pharmaceutical formulation used in clinical studies

No new data is submitted.

II.2 Non-clinical aspects

No new data is submitted.

II.3 Clinical aspects

Efficacy

No new data is submitted.

Safety

Study A1481276

This phase 2 study was a single-arm, single-centre study to investigate safety and efficacy of sildenafil in near-term and term newborns with PPHN. The planned study subjects were neonates (≥34 week gestational age and aged ≤ 72 hours) who had PPHN.

Study Objectives

Efficacy: The primary objective of the study was to determine the efficacy of IV sildenafil in near term and term newborns with PPHN or with hypoxic respiratory failure and at risk for PPHN. The primary measure of efficacy was the reduced need for iNO and extracorporeal membrane oxygenation (ECMO).
Safety: To assess the safety and tolerability of IV sildenafil in the before-mentioned population.
Pharmacokinetics (PK): To further characterize the PK of sildenafil in this population.
Long-term survival: Patients who completed Study A1481276 were to be enrolled in a long term follow-study, A1481283.

Study Design

This was a non-randomized, single arm, single center, open label study in male and female neonates (≥34 week gestational age and aged ≤ 72 hours). All subjects had to receive sildenafil. Forty subjects who were naïve to iNO were planned to be enrolled in the study. The subjects were identified and screened within 72 hours of birth.
Dose. Subjects who were eligible at screening received a loading dose of 0.1 mg/kg of IV sildenafil citrate given over 30 minutes, followed by a continuous maintenance dose consisting of an IV infusion of 0.03 mg/kg/hr for up to 14 days. There were 2 follow-up visits at 7±3 days and 28±3 days post end of treatment.
The outcomes of a control group of PPHN patients (who were not study subjects) identified from the Great Ormond Street Hospital (GOSH) database were to be analyzed in conjunction with the subjects in this study. Long term safety and neurological development of subjects were to be assessed during regular paediatric check up appointments at GOSH at 12 and 24 months after the end of study treatment. This is covered by a separate protocol, A1481283.

Inclusion Criteria. Subjects aged ≥34 week gestational age and aged ≤ 72 hours at screening with PPHN or hypoxic respiratory failure associated with either idiopathic PPHN or meconium aspiration syndrome

or sepsis or pneumonia; OI >15 and <60 (calculated using blood gases taken approximately 30 minutes apart prior to commencement of study treatment infusion); and screening echocardiogram to confirm presence of pulmonary hypertension (performed within 24 hours of admission to GOSH) were eligible to participate in this study.

Exclusion criteria were subjects already receiving iNO on referral; who had prior or immediate need for full cardiopulmonary resuscitation or ECMO, life-threatening or lethal congenital anomaly; large left-to-right intracardiac or ductal shunting (diagnosed from echocardiogram on admission to GOSH); clinically significant active seizures; bleeding concurrent medication/therapy at any time prior to screening.

Incidence of treatment failure was the ***primary efficacy endpoint***, which was defined as the incidence of iNO or ECMO at any point from initiation of sildenafil to Day 14 visit.
Safety data including AEs, laboratory tests and vital signs, were to be evaluated using descriptive statistics and presented using the Safety Analysis Set (defined as all subjects enrolled in the study).

Results
Subject Disposition. A total of 4 subjects were enrolled, assigned to the study treatment and analyzed for safety (AEs). Of these, 1 subject completed the study without the need for iNO or ECMO; and 3 subjects discontinued the study during the maintenance period. One subject discontinued due to AE of reduced cardiac function, one subject died due to PPHN and congenital pneumonia, and one subject was withdrawn as the subject did not meet entrance criteria.

No *Efficacy Pharmacokinetic, Pharmacodynamic* are available due to early termination.

Safety Results. All subjects in the study had 1 or more AE. Overall, 19 TEAEs and 12 non-TEAEs were reported during the study. The most frequently reported TEAEs were from the respiratory, thoracic and mediastinal disorders, system organ class (6 TEAEs in 3 subjects). The majority of TEAEs were mild (8 TEAEs) or moderate (6 TEAEs) in severity. Two (2) subjects reported 3 SAEs: bradycardia (one subject), persistent fetal circulation and congenital pneumonia (one subject). All SAEs were considered as not related to the study treatment by the investigator. One (1) subject (died due to 2 fatal SAEs: persistent fetal circulation and congenital pneumonia. Two subjects permanently discontinued the study: one subject discontinued due to AE of cardiac disorder, which was considered as not related to the study treatment; and one subject discontinued due to death (SAE).

Applicant's Conclusion
Due to evolved standard of care and widespread use of iNO at early signs of hypoxic respiratory failure or PPHN, the clinical relevance of study A1481276 came into question. Dialogue with PDCO of the EMA led to terminating the study prematurely. Only 4 subjects were enrolled and had received study treatment at the time of termination of study. The salient findings from the 4 subjects enrolled in this prematurely terminated study are:

- One subject completed the study without the need for iNO; 3 subjects discontinued from the study.
- The 4 subjects experienced 19 TEAEs and 12 non-TEAEs; majority of TEAEs were mild or moderate in severity.
- Two subjects experienced 3 SAEs: bradycardia in 1 subject; persistent fetal circulation and congenital pneumonia in other subject.
- One subject died due to 2 fatal SAEs: persistent fetal circulation and congenital pneumonia.
- One subject permanently discontinued the study due to an AE, cardiac disorder, which was considered as not related to the study treatment.

Intravenous sildenafil has the potential to be of value when administered to paediatric patients who have been diagnosed with PPHN. This is currently being investigated in Study A1481316. Results from the PPHN studies A1481157, A1481276, A1481283, and A1481316 will be submitted in a variation to include the results of these studies in the SmPC.

V. CHMP OVERALL CONCLUSION AND RECOMMENDATION

Revatio is approved for paediatric PAH since 2011. The current report concerns the premature termination of study A1481276 conducted in patients with PPHN. This study was part of the agreed PIP. The study was terminated due to slow recruitment considering that PPHN patients are more early administered iNO than before, making recruitment of iNO naïve patients difficult. This is also in line with the paediatric addendum to *CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension EMA/CHMP/213972/2010* which states that as nitric oxide (NO) is an authorized therapy for PPHN mainly add-on trials or trials in patients failing treatment with NO should be considered.

Available data from the study are too limited and do not allow any assessment of the potential use of Revatio IV in this indication.

The results of study A1481316 are awaited.

Based on the above, no update of the SmPC is considered necessary.

The premature termination of study A1481276 conducted in patients with near-term and term children with PPHN is acceptable within the context of current use of NO and does not influence the current benefit/risk of Revatio. No update of the SmPC is needed.

Further results from other studies in PPHN are awaited as follows.

According to the MAH, results from the PPHN studies A1481157, A1481276, A1481283, and A1481316 will be submitted which will allow further assessment of the use of Revatio in PPHN patients.