28 January 2016
EMA/CHMP/68991/2016
Committee for Medicinal Products for Human Use (CHMP)

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

Revatio

International non-proprietary name: sildenafil

Procedure No. EMEA/H/C/000638/P46/049.1

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

On 13 July 2015, the MAH submitted a completed paediatric study A1481304 for Revatio, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure P46.

A short critical expert overview has also been provided. Following the assessment, the MAH was requested to address 2 points. The responses are discussed on pages 7-8, and are considered satisfactorily solved.

2. Scientific discussion

2.1. Information on the development program

The indication for paediatric PAH was approved in the EU in May 2011 and was based on data from a pivotal clinical study (A1481131) and its extension study (A1481156), which included 234 paediatric patients with pulmonary hypertension and with a median treatment duration of 1696 days (~ 4.5 years). A third study (A1481134) has also been conducted in children with pulmonary hypertension after corrective cardiac surgery. An additional study (A1481252) was conducted in Japanese subjects with PAH who were treated with sildenafil.

The subject of this report is study A1481304, which was a local (India), open-label access study with sildenafil citrate in paediatric subjects with PAH who completed Study A1481156.1

2.2. Information on the pharmaceutical formulation used in the study

Patients received 20 mg sildenafil tablets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study A1481304, which was conducted in paediatric subjects with PAH to derive clinical benefit from continued treatment with sildenafil citrate. This study was conducted in patients who completed Study A1481156.

2.3.2. Clinical study

Study A1481304

Description

Study A1481304 was a local, open-label access study with sildenafil citrate in paediatric subjects with PAH who completed Study A1481156. The end-of-treatment visit for Study A1481156 was considered

as Visit 1 for Study A1481304. The study involved an initial visit followed by visits at a frequency defined by the Investigator's routine standard care. The follow-up contact was performed according to the Investigator's judgment and as necessitated by the drug supplies. All subjects returned to the clinic every 3 months for drug supplies and documentation of AEs and serious adverse events (SAEs).

Methods

Objective(s)

The primary objective was to provide sildenafil citrate therapy to the paediatric subjects who had completed Study A1481156 for the treatment of PAH and were judged by the Investigator to derive clinical benefit from continued treatment with sildenafil citrate. The study medication was to be supplied as long as the Investigator felt that the subject continued to derive benefit from the treatment.

Study design

Study population / Sample size / endpoints

All the subjects enrolled in the study received the recommended dose of 10 mg TID for subjects with body weight ≤20 kg, 20 mg TID for those with body weight >20 kg and 20 mg TID for subjects of 18 years of age and older regardless of body weight. Sildenafil citrate tablets were to be taken approximately 6 to 8 hours apart, with or without food.

A total of 4 subjects who completed Study A1481156 were enrolled in Study A1481304 and received 20 mg TID of sildenafil citrate as daily dose for approximately 21 months during the study. Of the 4 subjects, 3 were females and 1 was male, and all were of Asian-Indian origin. Subjects were aged between 16.2 and 25.1 years.

The primary end point was to provide sildenafil citrate to subjects completing Study A1481156 and who were judged by the Investigator to derive clinical benefit from continued treatment with sildenafil citrate. The study medication was to be supplied as long as the Investigator felt that subject continued to derive benefit from the treatment.

Results

All 4 subjects (aged 16.2 to 25.1 years) with PAH received 20 mg TID sildenafil for compassionate use for 17.8 to 18.3 months.

CHMP's comment

All 4 patients have equal treatment duration of 18 months. It is however unclear why that period is similar and if patients are continued to be treated under this compassionate use program (**LoQ**). It is also not clear why a patient above 18 years would be included in the current paediatric program (**LoQ**).

Efficacy results

New efficacy data did not come available with this study.

Safety results

A total of 3 out of 4 subjects experienced 8 treatment-emergent adverse events (TEAEs). The majority of the TEAEs (5) were reported for 1 subject (Subject 10021002), see table below.

Table 1. Overview of Treatment-Emergent Adverse Events: Safety Population

Subject No.	Preferred Term	Causality
10021001	Cough	No data
10021002	Pyrexia	Not related
	Nasopharyngitis	Not related
	Cough	Not related
	Rhinitis allergic	Not related
	Lower respiratory tract infection	Not related
10021003	Headache	No data
	Intermittent headache	No data

Source: A1481304 Clinical Study Report - Section 16.2, Listing 16.2.7.

All but 3 TEAEs were assessed by the Investigator as not related to the study medication, and for 3 TEAEs no causality relationship was provided. All TEAEs and the SAE were resolved at study completion. The severity of the TEAEs was not assessed by the Investigator.

Subject 10021002 experienced a lower respiratory tract infection, which was assessed by the Investigator as non-serious. However, upon review of the AE, the Sponsor assessed the event as serious based on interpretation of the Medical Dictionary for Regulatory Activities (MedDRA) List of Critical Terms. The Investigator considered the SAE to be not related to the study medication.

None of the subjects died during the study and no significant AEs occurred (see Table 3).

Company conclusion on benefit / risk

The safety data obtained from the sildenafil citrate compassionate-use study is consistent with the data obtained in other adult and paediatric PAH studies. The MAH is of the opinion that the paediatric results do not change the favourable risk/benefit relationship for paediatric patients and do not warrant any change to the product label.

2.3.3. Discussion on clinical aspects

No new information on the use of sildenafil in a paediatric population has come to light from this small study. The approved clinical doses have been used. The patients received doses in the lower dose range, i.e. 20 mg TID, used in the original paediatric study from which these patients were recruited. This is appropriate as in that long term paediatric extension study, an increase in deaths was observed in patients administered sildenafil at the higher dose range.

3. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Are these patients continued to be treated with sildenafil in the framework of this compassionate use program?
2. The age range of the recruited patients is from 16.2 to 25.1 years, indicating that some of them may not fall under the paediatric regulation. The MAH is requested to clarify.

The timetable is a 30 day response timetable with clock stop. The MAH should submit the responses **within 1 month.**

4. MAH responses to Request for supplementary information

Question 1:

Are these patients continued to be treated with sildenafil in the framework of this compassionate use program?

Applicant's Response:

The patients from Study A1481304 are no longer being treated with sildenafil in the framework of a compassionate use program managed by Pfizer. Once the study was terminated in August 2014, the patient's primary physician assumed responsibility for their continued treatment. Decisions regarding a patient's treatment program rest with their primary physicians.

CHMP's Response.

Issue resolved.

Question 2:

The age range of the recruited patients is from 16.2 to 25.1 years, indicating that some of them may not fall under the paediatric regulation. The MAH is requested to clarify.

Applicant's Response:

Study A1481304 was a compassionate use study in which physicians could continue to treat their patients with sildenafil if they determined that the patients had responded to sildenafil in the Revatio program conducted in paediatric patients with PAH. This program began with Study A1481131, a short-term, double-blind, placebo-controlled study of sildenafil in patients aged 1 to 17 years that included 16 weeks of treatment. Subsequent to this study, patients could enter Study A1481156, which was an open-label, long-term extension study for the continued assessment of the safety of the use of sildenafil in paediatric patients with PAH. Patients in this study were treated for many years (up to 7-8 years) as the study was to be continued until sildenafil was approved for use in the treatment of paediatric PAH. When Study A1481156 was terminated in late 2012, patients who participated in this study, and resided in countries where sildenafil was not available for use, were given the opportunity to continue to receive sildenafil under the direction of their physician who had been an investigator in the study. The provision of sildenafil to these patients could have been in the form of a compassionate use study or program depending on the regulations in the individual country. In India, the provision of sildenafil needed to be within a study and A1481304 was initiated. Pfizer was committed to providing the drug to patients with PAH who, in the physician's opinion, had responded to sildenafil and could not receive the drug locally. As a consequence, some of the patients who had originally entered Study A1481131 under the age of 18, and continued to receive treatment with sildenafil in Study A1481156

and A1481304, became adults during the prolonged period of treatment, but remained in the A1481304 study until it concluded. The patients were initially recruited into A1481131 when they were under the age of 18, but became older than 18 during the period of time that the studies were conducted.

CHMP's Response.

Issue resolved.

5. CHMP’s overall conclusion and recommendation

The submitted study results do not change the benefit-risk of sildenafil in children, if used at the approved clinical dose. The applicant satisfactorily addressed the additional questions.

☒ **Fulfilled:**

☐ **Not fulfilled:**