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Assessment report

Revatio

International non proprietary name: sildenafil

Procedure No. EMEA/H/C/000638/X/0037

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

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LIST OF ABBREVIATIONS

AUC	Area Under the Concentration-Time Curve
CI	Confidence Interval
Cmax	Maximum Observed Concentration
DDPS	Detailed Description of the Pharmacovigilance System
EMA	European Medicines Agency (EMA)
EP	Extemporaneously prepared
EU	European Union
GCP	Good clinical practice
ICH	International Conference on Harmonisation
HPLC	High-pressure liquid chromatography
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PDCO	Paediatric Committee
Ph Eur	European Pharmacopoeia
PIBA	Press-in bottle adaptor
PL	Package leaflet
POS	Powder for Oral Suspension
RMP	Risk Management Plan
SPC	Summary of Product Characteristics
TID	Three times a Day
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Ltd. submitted on 5 May 2011 an application for the extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Revatio 10 mg/mL, powder for oral suspension, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2, intend c) and d) of the Commission Regulation (EC) No 1234/2008.

Pfizer Limited is already the Marketing Authorisation Holder for Revatio 20 mg film-coated tablets and Revatio 0.8 mg/mL solution for injection (EU/1/05/318/001-002).

Revatio was designated as an orphan medicinal product EU/3/03/178 on 12/12/2003. Revatio was designated as an orphan medicinal product in the following indication: Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. The calculated prevalence of this condition was 1 per 10,000 EU population.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/114/2011 for the following condition(s):

- Treatment of Pulmonary Arterial Hypertension.

on the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant referred to the previously submitted critical report addressing similarity with authorised orphan products. The CHMP confirmed that the similarity assessment performed as part of variation EMEA/H/C/000638/II/0028 is still valid. The scope of this variation was to extend the indication to paediatric patients with pulmonary arterial hypertension aged 1 year to 17 years old. The CHMP was of the opinion that Revatio is not similar to iloprost (Ventavis), treprostinil (Remodulin), bosentan (Tracleer), ambrisentan (Volibris) within the meaning of Article 3 of Commission Regulation EC No. 847/2000 (see annex 4.4).

Scientific Advice

The applicant did not seek scientific advice or Protocol Assistance at the CHMP for this line extension application.

Licensing status:

Revatio has been given a Marketing Authorisation in EU on 28 October 2005.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pieter de Graeff**

1.2. Steps taken for the assessment of the product

- The application was received by the EMA on 5 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2011. An updated Day 80 AR was circulated on 16 August 2011.
- During the meeting on 19-22 September, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 November 2011.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 December 2011.
- During the meeting on 16-19 January, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting of an extension of the Marketing Authorisation to Revatio 10 mg/mL, Powder for Oral Suspension , on 19 January 2012.
- A revised opinion was adopted by the CHMP via written procedure on 23 January 2012.

1.3. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.4. Conditions or restrictions with regard to the safe and effective use of the medicinal product

The Marketing Authorisation Holder (MAH) shall agree the details of a controlled distribution system for the 20 ml vial of Revatio 0.8 mg/ml solution for injection with the National Competent Authorities and must implement such programme nationally to ensure that prior to prescribing all healthcare professionals who intend to prescribe and/or dispense Revatio 0.8 mg/ml solution for injection are provided with the following:

- Information for healthcare professionals
- Copy of the Summary of Product Characteristics (SPC)
- Data Capture Form (DCF) designed to facilitate reporting of events of hypotension and associated problems

The Information for healthcare professionals should contain the following key elements:

- Information about the Pharmacovigilance Monitoring Programme regarding the potential risk of clinically relevant hypotension and related problems to be put into place with the use of the DCF.
- Information on the switch from the 50 ml vial to the 20 ml vial for Revatio 0.8 mg/ml solution

The Marketing Authorisation Holder shall agree the Information for healthcare professionals, and the healthcare professionals to be targeted, with the national competent authority of each Member State prior to the launch of the 20 ml vial of Revatio 0.8 mg/ml solution for injection in that country.

1.5. Other conditions

Pharmacovigilance system

The Marketing Authorisation Holder must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

2. Scientific discussion

2.1. Introduction

This application for an extension of marketing authorisation is for the introduction of a new pharmaceutical form and a new strength of Revatio suitable for paediatric use: Revatio 10 mg/ml powder for oral suspension (POS). This was discussed and agreed with the Paediatric Committee (PDCO) EMEA-671-PIP01-09. The already existing presentations, Revatio 20 mg film-coated tablet and Revatio 0.8 mg/mL solution for injection, were authorised in the EU on 28 October 2005 and 24 September 2009, respectively.

The therapeutic indication for the Revatio 10 mg/ml powder for oral suspension is the same as for the authorised 20 mg tablets:

Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Paediatric population
Treatment of paediatric patients aged 1 year to 17 years old 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.

The Revatio solution for injection is only indicated for adults.

In order to facilitate the administration of Revatio in paediatric population, the applicant was requested by the PDCO and the CHMP to develop an alternative formulation. The powder for oral suspension was considered to be the most appropriate formulation for use in children below 6 years and who cannot swallow the tablets. The preparation of an extemporaneous suspension from the tablets was approved as an interim solution until the age appropriate formulation was available. Consequently the MAH is recommended to delete the information on crushing of tablets to prepare a suspension for paediatric use once the new POS is marketed in the EU. The MAH should aim at shortening the transition period as much as possible to enable patients and prescribers the use of the powder for oral suspension in children.

The product information of Revatio has been updated to include the 10 mg/ml powder for oral suspension presentation. In addition, the product information has been revised to comply with the latest QRD guideline.

Within this application, the applicant has updated the detailed description of the system of pharmacovigilance (DDPS) and a RMP waiver for this line extension has been submitted.

2.2. Quality aspects

Introduction

Revatio powder for oral suspension 10 mg/mL is presented as a white to slightly pink powder packaged in a 125 mL type III amber glass bottle for reconstitution with water. The bottle is filled with 32.27 g of dry powder blend to be constituted with the addition of 90 ml of water yielding approximately 112 ml of constituted suspension. Upon constitution, a 10 mg/mL suspension is achieved that is adequate to provide a 30 day supply of a 10 mg dose, or a 15 day supply of a 20 mg dose.

In addition to the bottle, a 30 mL cup for constitution of the formulation is provided, along with a press-in bottle adapter (PIBA) and syringe to ensure accurate dosing.

The active substance is sildenafil citrate. The list of excipients can be found in section 6.1 of the SmPC.

2.2.1. Active Substance (to be changed in the EPAR to "Active Substance")

Sildenafil citrate, the active substance used in the manufacturing of the Revatio powder for oral suspension is identical to the active substance used in the manufacturing of the currently authorized Revatio tablet formulation. For data on the active substance reference was made to the Module 3.2.S of the initial marketing authorisation of the 20 mg tablets and subsequent quality variations.

2.2.2. Finished Medicinal Product (To be changed in the EPAR to "Medicinal Product")

Pharmaceutical Development

The aim of the pharmaceutical development was to develop a dosage form appropriate for paediatric use. In order to minimize the taste challenges of an oral solution and the physical stability risk of a ready to use suspension, the powder for oral suspension (POS) platform was progressed and agreed by the PDCO as the most appropriate dosage form.

The paediatric formulation is a dry powder blend that is constituted into a multidose suspension suitable to provide the recommended doses for paediatric patients aged 1 year to 17 years old of 10 mg (1 ml of suspension) three times a day for patients ≤ 20 kg and 20 mg (2 ml of suspension or 1 tablet) three times a day for patients > 20 kg. The 112 ml volume is indeed sufficient for one month (3 x 1 ml for 30 days) or 15 days (3 x 2 ml for 15 days.

Different factors were studied during the development of the new pharmaceutical form: pH of the suspension, choice and concentration of the buffer, preservative concentration, suspending agent concentration, robustness of the suspension and caking of the powder blend. The effect of viscosity on resuspendability and accurate dosing has been tested over the whole viscosity range observed for the product. Acceptable palatability has been substantiated.

Due to the bitter taste of sildenafil citrate, sweeteners (sucralose and sorbitol) and grape flavour are used to mask the taste. The desired pH of the suspension is achieved by a buffer and the pH is selected to ensure stability of the sildenafil citrate as well as effectiveness of the preservative, sodium benzoate, which is utilized to meet the quality requirements for the multidose product. The formulation is packaged in an amber glass bottle with a polyethylene lined closure to provide adequate stability to ensure shelf-life.

All excipients used in the manufacture of Revatio POS are of pharmacopoeial or food grade.

As the active substance is not highly soluble and has a low oral bioavailability (41%) a BCS-based biowaiver was not accepted and a bioequivalence study with the POS formulation and the registered 20 mg tablets was requested and submitted by the applicant (see section 3.3.2).

Adventitious Agents

Revatio POS 10 mg/mL does not contain materials of animal or human origin.

Manufacture of the Product

Sildenafil citrate POS, 10 mg/ml is manufactured using a blend-mill-blend manufacturing process. This process was selected because it is a standard process and the commercial site is familiar with it in the manufacture of other products. Development studies were performed with small scale batches (2kg) to select blend speed, blend fill volume, mill speed and mill screen opening site.

Blend process scale up (content uniformity on four batches) and the bottle filling process (bottle fill weight and potency and cap torque on two batches) were studied on 200 kg batches manufactured at the proposed site. Additionally, three registration batches of 200 kg have been manufactured at the proposed site with review of blend uniformity and bottle fill process (by fill weight and potency testing).

No critical steps or intermediates have been identified.

The manufacturing process demonstrated to be reproducible and provides a finished product that complies with the finished product specifications.

In view of the standard manufacturing process and the results of the manufacturing process development provided it is considered acceptable to conduct the process validation study in accordance with the protocol submitted on the first three production scale batches of the product, post-approval.

Current commercial batch size is anticipated to be 200 kg but may be adjusted based on expected market demand.

Sildenafil citrate POS, 10 mg/ml, is presented in an amber glass bottle (USP-type III) with a polyethylene (PE) liner closure, a press-in bottle adaptor (PIBA), a 3 ml oral dosing syringe, and a 30 ml cup for reconstitution. The oral dosing syringe bears calibration marks that have been demonstrated to be accurate for delivering the required volumes of the constituted POS (1ml and 2 ml for the 10 mg and 20 mg doses respectively). Uniformity of mass of delivered dose was verified.

The materials used for the LDPE closure liner, syringe, PIBA and cup comply with the EU food Directive 2002/72/EC. The cup, oral syringe and PIBA meet the requirements of Ph Eur 3.2.2. 'Plastic containers and closures for pharmaceutical use'. The oral syringe is CE marked. A declaration on compliance with Medical Devices EC Directive 93/42/EEC article 11 Section5 and Annex VII, and with the measuring requirements of Annex V has been provided. A declaration on compliance with that Directive has also been provided for the cup.

Product Specification

The finished product release and shelf-life specifications for Revatio POS, 10 mg/mL include tests for appearance, fill weight and water content of powder (Ph. Eur.); whereas specifications for the constituted suspension include: appearance, identification (HPLC), assay (95.0%-105.0% of label claim), impurities (HPLC-not routinely), preservative content (HPLC), uniformity of dosage units (Ph. Eur.), pH and microbiological limits (Ph. Eur.-not routinely).

The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled.

Full batch analysis data have been provided for three registration batches of the POS suspension. Batch analysis results comply with the proposed specifications and confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the Product

Stability studies have been performed in accordance with ICH guideline Q1A (R2) on three batches of sildenafil citrate POS, 10 mg/mL packaged in 125 mL Type III amber bottles with low density polyethylene (LDPE) lined plastic closure. Data included up to 18 months 25°C/60% RH and 30°C/75% RH, and up to 6 months data at 40°C/75% RH and refrigerated storage conditions. In addition, an in-use stability study was performed, and the photostability of one batch was evaluated in accordance with ICH guideline Q1B.

The stability batches were made and packaged at the commercial manufacturing site. The batch sizes were approximately 200 kg and are of equivalent size to that of the commercial product.

The stability samples were evaluated for appearance and water content (before constitution) and appearance, redispersability, reconstitution time, assay, impurities, preservative content, pH and viscosity after constitution. Microbial quality was also tested.

The analytical procedures used to monitor those characteristics are identical to the ones applied for release testing, except appearance and water content methods. The methods used were validated and demonstrated to be stability indicating.

Based on the long term stability data and supportive data in accelerated conditions, the proposed shelf-life of 2 years, stored not above 30°C in the original packaging to protect from moisture for the powder for oral suspension, and an in-use shelf-life of 30 days, stored not above 30°C and "do not freeze" for the reconstituted suspension are acceptable.

A commitment is made to place the first three commercial scale batches of sildenafil citrate POS, 10mg/mL on long term stability at 30°C/75%RH.

In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.3. Discussion on chemical, pharmaceutical and biological aspects

Revatio POS is manufactured using the same active substance as the already authorised 20mg tablets.

Information on development, manufacture and control of the medicinal product has been presented in a satisfactory manner.

The results of tests carried out on the finished product indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The quality of this medicinal product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

Pharmacokinetic study A1481293

A bioequivalence study has been performed, comparing sildenafil citrate powder for oral suspension (10 mg/mL) with the registered 20 mg Revatio immediate release tablet and 2 x 10 mg sildenafil citrate immediate release tablets.

Study Design

The study was conducted as a three-way, three period, 6-sequenses, single dose cross-over study in healthy male (14) and female (28) subjects) aged 18 – 54 years, BMI 17.5 – 30.5 kg/m^2). Before the products were administered the subjects fasted for at least 8 hours. The products were administered with 240 ml water. Blood samples were taken upon administration at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 14 hours.

Test and reference products

Test: Sildenafil powder for suspension, 10 mg/ml, batch 10-082576.

Reference: Sildenafil 10 mg tablets, batch 07-061004.

Analytical methods

Sildenafil was determined in plasma with a validated LC-MS/MS method. The calibration curve range from 1.0 ng/ml till 500 ng/ml. Precision and accuracy were in compliance. The long term stability in the biological matrix was tested over a period of 1275 days. In total 180 incurred samples were analyzed. Analytical method seems adequate to determine sildenafil in plasma accurately.

Results

The table below describes the pharmacokinetic parameters observed in the A1481293 study.

Table 1. Pharmacokinetic parameters of sildenafil and 90% confidence intervals

Parameter (units)	Adjusted Geometric Means		Ratio of Adjusted Means[a]	90% CI
	Test	Reference		
Sildenafil 20 mg (2 mL) POS (Test) versus Revatio 1 x 20 mg Tablet (Reference)				
AUC_{inf} (ng*h/mL)	166.6	184.0	90.57	(85.54, 95.90)
AUC_{last} (ng*h/mL)	161.3	178.6	90.35	(85.17, 95.84)
C_{max} (ng/mL)	71.91	75.74	94.95	(85.48, 105.46)
Sildenafil 20 mg (2 mL) POS (Test) versus Sildenafil 2 x 10 mg Tablets (Reference)				
AUC_{inf} (ng*h/mL)	166.6	184.9	90.10	(85.00, 95.50)
AUC_{last} (ng*h/mL)	161.3	178.3	90.51	(85.32, 96.01)
C_{max} (ng/mL)	71.91	76.12	94.47	(85.05, 104.93)
Sildenafil 2 x 10 mg Tablets (Test) versus Revatio 1 x 20 mg Tablet (Reference)				
AUC_{inf} (ng*h/mL)	184.9	184.0	100.52	(94.83, 106.55)
AUC_{last} (ng*h/mL)	178.3	178.6	99.82	(94.10, 105.89)
C_{max} (ng/mL)	76.12	75.74	100.50	(90.48, 111.63)

Source: Table 14.4.3.2., A1481293 CSR
CI = confidence interval; POS = powder for oral suspension.
[a] The ratios (and 90% CIs) were expressed as percentages.

2.3.3. Discussion and conclusion on clinical pharmacology

The pharmacokinetic variables after administration of the three formulations are comparable. The 90% confidence intervals in the comparison with the POS formulation are well within the acceptance criteria of 0.80 – 1.25 for the rate and extent of absorption. Therefore bioequivalence can be considered as established.

2.4. Update of the product information

Revatio product information has been updated to include the powder for oral suspension presentation. In addition, the product information has been revised to comply with the latest QRD guideline.
The MAH is recommended to delete the information on crushing of tablets to prepare a paediatric use formulation once the new POS is effectively marketed in the EU.

User consultation

The Package Leaflet (PL) for Revatio 10 mg/ml Powder for Oral Suspension (Sildenafil) has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.
Overall the results demonstrate that the PL meets the requirements set for user testing and the user test is found to be acceptable.

2.5. Detailed description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance of Pfizer, version 3.0, dated 9 November 2010. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.6. Risk Management plan

The Applicant submitted a Risk Management Plan Waiver, dated 2 May 2011. The current RMP waiver applies to this MAH application, which is being submitted for the Revatio line extension i.e. the powder for oral suspension for use in paediatric PAH patients. This waiver was considered acceptable by the CHMP.

An updated Revatio RMP v5.0 was included in the application for a new paediatric indication submitted to EMA on 12 February 2010. During the EMA review process, this RMP version has been updated. The assessment of the updated RMP (v5.3 and 5.4) is included in the type II variation EMEA/H/C/638/II/040 which is currently under evaluation.

4. BENEFIT RISK ASSESSMENT

This new POS of Revatio has been developed to provide a formulation suitable for paediatric use (children from 1 to 6 years old), especially for those unable to swallow the 20 mg tablets.

The CHMP concluded that the benefit-risk balance of this line extension is positive.

The overall Benefit risk of Revatio is positive.

Proposed list of recommendations:

1. The MAH is recommended to delete the information on crushing of tablets to prepare a paediatric use formulation once the new POS is effectively marketed in the EU.

2.7. Recommendation

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Revatio is not similar to iloprost (Ventavis), treprostinil (Remodulin), bosentan (Tracleer), ambrisentan (Volibris) within the meaning of Article 3 of Commission Regulation EC No. 847/2000 for the same therapeutic indication. See annex 4.4.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of the new pharmaceutical form for Revatio in the treatment of:

- Adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.
- Paediatric patients aged 1 year to 17 years old 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 (See section 5.1).

was favourable and therefore recommended the granting of the extension of the marketing authorisation.