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Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR REVATIO

International non-proprietary name/Common name: sildenafil

Procedure No. EMEA/H/C/638/X/0019

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. SCIENTIFIC DISCUSSION

1.1 Introduction

Sildenafil citrate is a potent and specific inhibitor of phosphodiesterase type 5 (PDE5). It was originally approved in 1998 for the treatment of male erectile dysfunction (MED), under the trade name Viagra, in both the United States (US) and the European Union (EU) (EMEA/H/C/202). Later, sildenafil citrate was approved for: *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* under the trade name Revatio, in the USA and the EU in 2005.

Pulmonary hypertension is a rare, progressive and life threatening disease. The currently available oral therapies have all been approved for daily administration on a long-term basis. However, patients with PAH may find themselves in clinical settings where they are temporarily unable to take oral medications or unable to absorb medications enterally. This includes clinical scenarios such as acute gastrointestinal disturbance, malabsorption due to complications of connective tissue disease, sudden illness involving diarrhoea and vomiting or peri-operatively. Especially in the latter cases, PAH patients are at a higher risk for major complications including pulmonary hypertensive crisis, right-sided heart failure and cardiac arrest. Review of the MAH's clinical trial database did not suggest that short-term interruption of oral therapy was associated with immediate or rapid worsening of the symptoms of PAH in patients who had otherwise been on stable therapy. However, it is potentially disadvantageous to the patient that, in such circumstances, with no other sildenafil formulation currently available, the physician has no option but to either interrupt treatment, even if continuation of therapy was felt to be in the patient's best interest, or to initiate an alternative therapy which the patient may not be able to tolerate. For these reasons, maintenance of effective therapy can be considered important.

The Marketing Authorisation Holder (MAH) filed an extension application for Revatio 0.8 mg/ml, solution for injection, in accordance with Annex II of the Commission Regulation EC No 1085/2003. This application meets the criteria of a new pharmaceutical form, strength and route of administration for Revatio 20 mg tablets.

The proposed therapeutic indication for Revatio solution for injection is:
"Revatio solution for injection is for the treatment of patients with pulmonary arterial hypertension who are currently prescribed oral Revatio and who are temporarily unable to take oral medicine, but are otherwise clinically and haemodynamically stable.
Revatio (oral) is indicated for treatment of 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."

1.2 Quality aspects

Introduction

The medicinal product Revatio 0.8 mg/ml solution for injection is presented as a vial containing 50 ml clear, colourless, sterile solution. Each 50 ml vial contains 40 mg of sildenafil (as citrate), therefore 12.5 ml contains 10 mg of sildenafil. The excipients present in this medicinal product are glucose and water for injections. The medicinal product is packed in a 50 mL clear Type I glass vial with a chlorobutyl rubber stopper and aluminium overseal, and is for single use only.

Active Substance

The active substance, sildenafil citrate, is a known active substance; however, it is not described in the European, British or US Pharmacopoeia. The active substance used in the manufacturing of Revatio 0.8 mg/ml solution for injection is identical to the one used in the manufacturing of the currently authorized presentation; Revatio 20 mg film-coated tablets (EU/1/05/318/001). Therefore the applicant

referred to the active substance information which was submitted for the already authorised film-coated tablets. Only limited new information on the active substance has been submitted.

The active substance manufacturing process is the same as for the Revatio tablets, except that also the endotoxin limit of water is controlled in the current manufacturing process.

The active substance specifications are similar to the already marketed Revatio tablets, except for stricter limits for a specified impurity and total amount of impurities and with additional requirements for endotoxin limit. The specifications are considered acceptable and comply with the European guidelines. Batch analytical data demonstrating compliance with the active substance specifications have been provided for three pilot scale batches and for four additional batches manufactured during development and for clinical batches. No new stability data have been provided and reference is made to Revatio tablets for the stability data of the active substance.

Medicinal Product

- Pharmaceutical Development

Revatio solution for injection has been developed to offer an alternative pharmaceutical form and route of administration for patients unable to take the oral tablet. The aim was to develop a ready-to-use aqueous solution with minimal excipients and optimal physiological compatibility. Conventional excipients have been selected for this formulation; glucose as tonicity modifier and water for injections as vehicle. Furthermore, nitrogen is used as a processing aid. All excipients comply with the Ph. Eur. The glucose specifications include additional test for microbiological quality. The pharmaceutical development of the medicinal product has been adequately described, the choice of excipients is justified and their functions explained.
At the time of the opinion, there is one outstanding issue in relation to the vial size. Since the dose administered is only 12.5 ml and the medicinal product is for single use only, it is considered that a smaller vial size than the current 50 ml vials should be developed. The applicant has committed to replace the 50 ml vial by a 20 ml vial presentation containing a nominal fill volume of 12.5 ml (10 mg sildenafil) as a post-approval follow-up measure.

- Adventitious Agents

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product. Consequently, a theoretical risk of transmitting TSE can be excluded.

- Manufacture of the Product

The manufacturing process is a standard manufacturing process for solutions for injection. The process involves the following stages: bulk product compounding, filtration, filling into vials and terminal sterilization. The manufacturing process is adequately described and validated according to relevant European guidelines. Process validation data for this medicinal product have been presented for three commercial scale batches. An adequate manufacturing process validation scheme has been submitted and additional process validation for the filling process will be performed post authorization.

- Product Specification

The product specifications include adequate tests for appearance, identity, assay, degradation products, (sub-) visual particles, sterility, bacterial endotoxins, pH, uniformity of dosage units and extractable volume. The release and shelf life excipients are similar, except for the limit of a glucose derived degradation product. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial scale batches, demonstrating compliance with the release specifications.

- Stability of the Product

Stability data on the product have been provided for three full scale batches stored at 25°C/60% RH (36 months) and/or 30°/65% RH (36 months) and/or 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. In addition, one of these batches was stored at 50ºC/20%RH during 3 months and 5ºC during 36 months.
The batches were stored in Type I clear glass vial with chlorobutyl rubber stopper and aluminium overseal. No clear trends were observed at all storage temperatures, except for the content of one impurity. Although an increase was seen for that impurity over time, the amount remained within the proposed shelf life limits. Therefore, the proposed shelf life and storage condition are justified. In addition, the results of the photostability study and the temperature cycling studies sufficiently justify the absence of the additional storage conditions.
The stability data were generated by validated and stability indicating methods. Based on the stability data, the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The active substance used in the manufacture of the film-coated tablets is exactly the same as for the already authorized presentations.
The manufacturing process of the solution for injection, and excipients used are appropriate and well controlled. Appropriate finished product specifications have been set.
Batch analysis results show that the medicinal product can be reproducibility manufactured, compliant with the finished product specifications, and therefore the product should have a satisfactory and uniform performance in clinic. Stability data show that the medicinal product is stable until the end of the proposed shelf life.

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the benefit-risk- balance of the product. The applicant committed to resolve it as follow up measure(s) after the opinion, within an agreed timeframe.

1.3 Non-clinical aspects

Pharmacology

No new information regarding the pharmacology was provided which was acceptable as the pharmacology of sildenafil is well-known.

Pharmacokinetics

Absorption, distribution and excretion studies were not conducted in this extension application for intravenous administration, since most kinetic studies were performed for oral administration of Revatio. Three in vitro pharmacokinetic studies have been performed:

- In vitro metabolism of sildenafil by CYP3A4 and CYP3A7 [DM-04-148-39 (DM39)]
- In vitro metabolism of UK-92,480 in human liver microsomes: enzymology of UK-150,564 formation [DM-04-148-40 (DM40)].
- In vitro cytochrome P450 inhibition studies on CYP2B6 and CYP2C8 by sildenafil in human liver microsomes [DM-04-148-38 (DM38)].

These three new pharmacokinetic studies were not performed in compliance with GLP. The studies were however of sufficient quality.

Absorption: Comparison of Plasma Concentrations in Toxicology Studies and in Humans
According to the MAH, some of the information contained within this section has been previously submitted in the initial marketing authorization application. Some additional comparisons have been made to specifically support this Extension Application.

Given the species differences in plasma protein binding, it is considered appropriate to compare exposure in animals and humans using unbound plasma concentrations of sildenafil and UK-103,320 (a circulating metabolite formed by demethylation at the N-methyl-piperazine moiety).

Toxicokinetic samples were not collected during the intravenous toxicology studies; therefore, Cmax values have been extrapolated from intravenous pharmacokinetic studies in rat (4 mg/kg) and dog (1 mg/kg). Pharmacokinetic data have not been determined in clinical studies following a 10 mg three-times daily (TID) intravenous infusion of sildenafil over 5 minutes; therefore, exposure data has been calculated (study report "Two compartmental analysis of pharmacokinetics in Study 148-203") based on a 20 mg single intravenous infusion over 40 minutes from study 148-203.
Systemic exposure (in terms of AUC) following an intravenous dose of 10 mg TID over 5 minutes to human is projected to be similar to that following the recommended therapeutic oral dose of 20 mg TID (see section 2.7.2.3.4). Therefore, the chronic oral toxicology and human safety data support the extension application of Revatio® solution for injection (for intravenous use) in terms of AUC.

In terms of Cmax, systemic exposure following an intravenous dose of 10 mg TID to human is projected to be lower than that following 100 mg oral administration (sildenafil unbound Cmax; 22 ng/mL, UK-103,320 unbound Cmax; 13 ng/mL (previously submitted: Viagra® EMEA/H/C/000202)). Given the change, however, from oral to intravenous administration as a slow bolus injection (over 5 minutes), separate consideration has still been given to acute exposure as reflected by Cmax (see Table 1 and Table 2). At the no observed adverse effect level (NOAEL) in male and female rat and dog, the Cmax of sildenafil and UK-103,320 are substantially greater than that projected in human following a 10 mg intravenous dose (5 minute infusion). Thus, when data for both parent compound and UK-103,320 are considered, the exposure multiples (see Table 2) indicate a clear separation between clinical exposure in human up to the expected maximum clinical intravenous dose of 10 mg TID (over 5 minutes) and the exposure associated with toxicity in rat and dog.

Table 1. Projected Cmax values for sildenafil and UK-103,320 at NOAELs in toxicology species in comparison with projected human Cmax values following intravenous administration over 5 minutes

Species	Dose[a] (mg/kg)	Total Projected Cmax (ng/mL) [Unbound Projected Cmax (ng/mL)][b]	
		Sildenafil	UK-103,320
Rat (M)	4	2880 [144][c]	147 [16.2][c]
Rat (F)	4	2340 [117][c]	89.9 [9.9][c]
Dog (M and F)[d]	4	1128 [158][e]	72 [10.1][e]
Human	0.14[f]	203 [8.1][g]	13.5 [0.7][h]

M = Male; F = Female.
[a] No observed adverse effect level (NOAEL) dose in 1 month IV toxicology studies.
[b] Rat unbound fraction (fu) of sildenafil is 0.05 and UK-103,320 is 0.11. Dog fu of sildenafil is 0.14 and UK-103,320 is 0.14. Human fu of sildenafil is 0.04 and UK-103,320 is 0.05.
[c] Cmax values used from 4 mg/kg IV dose in rat PK study (previously submitted; EMEA/H/C/638).
[d] Data for male and female animals have been combined for dog since there is no evidence of a gender difference in pharmacokinetics.
[e] Extrapolated Cmax values calculated from Cmax values from 1 mg/kg IV dose in dog PK study (previously submitted; EMEA/H/C/638). Calculations: Sildenafil Cmax: 282 ng/mL multiplied by 4 = 1128. UK-103,320 Cmax: 18 ng/mL multiplied by 4 = 72 ng/mL.
[f] Human dose in mg/kg calculated assuming 70 kg bodyweight (10 mg TID).
[g] Human sildenafil Cmax data projected for 5 minute IV infusion (study report "Two compartmental analysis of pharmacokinetics in Study 148-203").
[h] Human UK-103,320 Cmax data used from study 148-203 assuming that the Cmax remains the same between the 40 and 5 minute infusion.

Table 2. Dose and unbound Cmax multiples for sildenafil and UK-103,320 based on NOAELs in toxicology species in comparison with projected human data

Species	Dose (mg/kg)	Dose Multiple	Unbound Cmax Multiples	
			Sildenafil	UK-103.320
Rat (M)	4	28.6	18	23
Rat (F)	4	28.6	14	14
Dog (M and F)	4	28.6	20	14
Human projection	0.14	NA	NA	NA

M = Male; F = Female; NA = Not applicable.

Distribution

No additional information was submitted in the extension application.

Metabolism

In vitro metabolism

The metabolism of sildenafil by CYP3A4 and CYP3A7 has been investigated using recombinant enzymes, with midazolam and fentanyl (CYP3A substrates) as comparators. All three substrates were metabolised by rCYP3A4 with the most rapid rate observed for midazolam, followed by sildenafil and slowest with fentanyl. By comparison, intrinsic clearance with rCYP3A7 was much lower for all three substrates, however the relative rates of metabolism for sildenafil and midazolam were reversed, suggesting sildenafil to be a better substrate for CYP3A7 than both midazolam or fentanyl. Thus, sildenafil is a substrate for CYP3A7, but intrinsic clearance in recombinant supersomes is approximately 25-fold lower than that of CYP3A4 (study DM39).

UK-150,564 is the N,N-de-ethylated metabolite of UK-092,480 in man. The formation of this metabolite has been studied in human liver microsomes and the cytochromes P450 enzymes mediating this transformation identified. In human liver microsomes the metabolic pathway was characterised by single enzyme kinetics with a Km of 20.97 μM. Further characterisation of UK-150,564 formation was investigated using specific CYP inhibitors in human liver microsomes. Incubations in the presence of furafylline, sulphaphenazole, benzylnirvarnol, and quinidine, inhibitors of CYPs 1A2, 2C9, 2C19, and 2D6 respectively, showed no significant inhibition of UK-150,564 formation. However, in the presence of the specific CYP3A4 inhibitor, ketoconazole, there was a significant reduction in UK-150,564 formation. Together, these data indicate that formation of UK-150,564 is mediated through CYP3A4 (study DM40).

In vitro inhibition
The potential for sildenafil to inhibit the activity of the drug metabolizing cytochrome P450 enzymes CYP2B6 and CYP2C8 has been studied *in vitro* in human liver microsomes. Sildenafil was demonstrated to be a weak inhibitor of cytochrome P450 activity with estimated IC_{50} values of >30 μM against each of the enzymes investigated (study DM38). Sildenafil is therefore unlikely to inhibit the metabolism of substrates for CYP2B6 and CYP2C8 in the clinic. Previously submitted studies showed IC_{50} values >300 μM for CYP1A2, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The IC_{50} value for CYP2C9 was 150 μM (Ki 80 μM).

Excretion
No additional information was submitted in the extension application.

Toxicology

No additional toxicology studies have been conducted for this application. Summaries were provided of intravenous repeated-dose studies in rats and dogs and of an intra-arterial local tolerance study in rabbits that were already present in the initial marketing authorisation application.

Repeat-dose toxicity
Intravenous studies that were performed in rats and dogs, in both species of 2 weeks and 1 month duration.

Rats
A noteworthy finding which was observed in intravenous studies in rats, compared to oral studies over the dose range 0.5-10 mg/kg was a slight increase in the incidence and severity of foci of myocardial inflammation at 4 mg/kg in the 1-month study relative to the concurrent control. Foci of myocardial inflammation varied from a minimal (grade 1) lesion, composed of small, rare foci of mononuclear cells surrounding occasional necrotic myocytes, to mild (grade 2) lesion, characterized by discrete coalescent foci with a linear shape. Mild lesions were located within the right ventricular wall only. These lesions were more often observed in males than in females, and appeared to have a slightly higher incidence in high-dose animals than in controls. The relationship of this finding to treatment is uncertain, given that similar changes were observed in controls and the absence of this finding in a 4-week or 6-month oral toxicity study (Study numbers 90143 and 91098 respectively).
The MAH considered the apparent increase in the incidence and severity of myocardial inflammation in the 1-month IV study as not a toxicological hazard to humans.

Dogs
The intravenous administration of sildenafil in a range-finding study at doses of 5 and 10 mg/kg produced liquid feces, an attenuation of the pupillary reflex and at 10 mg/kg, reddening of the conjunctiva and ear pinnae. An increase in heart rate occurred at 10 mg/kg, and to a lesser extent at 5 mg/kg. In the high-dose group, there were increases in plasma cholesterol and liver weight. In the pivotal 1-month study, sildenafil at doses up to 4 mg/kg produced no treatment-related effects, defining 4 mg/kg as the IV NOAEL in dogs.

Toxicokinetics
Toxicokinetics were not determined in the intravenous toxicology studies. However, the MAH has shown that minimal accumulation of sildenafil is expected in human. The safety is guaranteed by the fact that 80 mg oral dose t.i.d. was well tolerated in human and therefore no concern is expected by the dose of 10 mg i.v. t.i.d (comparable to 20 mg oral dose t.i.d.).

Local tolerance: Intra-arterial study in rabbits
A study examining intra-arterial tolerance after a single injection was conducted in rabbit (Study No. 91073). A group of 4 female rabbits received a single 0.5 mL injection of sildenafil at the maximum practicable concentration of 2 mg/mL in aqueous 5% mannitol via the left ear artery. In addition to the untreated contralateral ear which served as a control, a further group of 4 control rabbits was dosed with the vehicle alone. Half the animals were sacrificed on Day 3 and half on Day 21 with all ear

artery sites being examined microscopically. There was no evidence of treatment-induced local irritation at this 2 mg/mL concentration which represents 2.5 times the proposed clinical formulation strength (0.8 mg/mL).

Local tolerance was also studied in available repeated dose studies with intravenous administration. These studies showed no additional intolerance in sildenafil-treated injection sites compared to the control sites.

Antigenicity
Antigenicity of sildenafil was investigated in guinea pigs in the Viagra dossier following oral or subcutaneous administration. No evidence of antigenic potential was observed.

Studies on impurities
The bulk lots of sildenafil used in the toxicology studies had impurity profiles which embraced those of the compound tested clinically and the proposed commercialised product. Overall the sildenafil toxicology programme supports the drug substance specification limit for the specified impurity UK-263,909 of 0.3% maximum and the individual unspecified impurity limit of 0.1% maximum. According to the MAH, the 0.2% specification limit for the residual solvent 2-butanone is below the 0.5% justification threshold described in the International Committee of Harmonization (ICH) Guideline.

Ecotoxicity/environmental risk assessment

The MAH states that the i.v formulation is intended for use as a temporary replacement for oral administration and will not result in an increase in environmental exposure. Therefore, an environmental risk assessment is considered not necessary. A follow-up measure regarding the environmental risk assessment of Revatio for oral administration is still running. Extra studies above the information as already requested for Revatio for oral administration are not necessary.

Discussion on the non-clinical aspects

Three additional studies were provided for this extension application, which would already have been valuable for the approval of Revatio for oral use, as they investigate the metabolism of sildenafil, either after oral or i.v. application. The additional studies for this extension application did not contain information on the comparison in plasma (or tissue) kinetics after oral and i.v. administration. However, as a good comparison was provided between oral and i.v. administration in humans, additional animal studies are not required. The maximum plasma concentration and systemic exposure following oral administration were 30% and 41%, respectively, compared to i.v. administration. In addition, based on the discussion provided regarding comparison of exposure levels for unbound sildenafil in rat, dog and human from pharmacokinetic and toxicity studies, there is no reason to expect that the intravenous administration of sildenafil at the proposed dose of 10 mg TID would result in any new adverse effects in humans.

In all species studied, sildenafil is metabolised extensively. Up to five primary metabolic pathways were identified. In animals, qualitatively similar metabolic profiles were found as compared with man. UK-103,320 was present as a primary metabolite in plasma and excreta of all species examined. No significant human-specific metabolites were identified.

The only noteworthy finding which was observed in a 1-month intravenous study in rats, compared to oral studies over the dose range 0.5-10 mg/kg was a slight increase in the incidence and severity of foci of myocardial inflammation. This was considered not relevant, because no myocardial inflammation was observed in a study in which higher exposures were reached (oral 1-month study), and because there is no evidence that cGMP, of which the degradation is inhibited by sildenafil, acts as an inflammatory mediator. In dogs, no additional toxicity was observed in the i.v. studies compared to the oral studies that were conducted with sildenafil.

There was no evidence of treatment-induced irritation after a single intra-arterial injection in rabbits. Local tolerance was also studied in available repeated dose studies with intravenous administration. These studies showed no additional intolerance in sildenafil-treated injection sites compared to the control sites.

Antigenicity of sildenafil was investigated in guinea pigs following oral or subcutaneous administration. No evidence of antigenic potential was observed. Antigenic potential was not investigated following intravenous injection. However, if no antigenic potential was observed after subcutaneous injection, also no antigenic potential is expected following intravenous injection.

1.4 Clinical aspects

Introduction

The following table shows the 7 studies conducted for the development programme for Revatio IV in healthy volunteers (Studies A148-203, A148-208 and A148-215), adult patients (Pivotal study A1481024 and study A-148-301) and children (studies A1481134 and A1481157). Despite the MAH not seeking a paediatric indication, these 2 last studies provided additional safety data for the IV formulation.

Table 3. Studies relevant to the development programme for Sildenafil solution for injection

Study Protocol Nº	Study Population Design and objective	Treatment groups	Nº of subjects by treatment group	Demographics	Dosing regimen
A148-203	8 Healthy Volunteers. Single- blind four-way cross-over study to assess the safety, toleration, pharmacokinetics And pharmacodynamic effect on plasma cyclic GMP of sildenafil	Sildenafil IV (N = 8)	Randomized: 8 Treated: 8 Completed: 8	Sex: 8 M/0 F Mean Age: 25 yrs Race: W/B/O: 7/1/0	Four single IV infusions (20, 40, 80 mg sildenafil, and placebo) given as **40 minute infusions**. (washout period: 7 days)
A148-208	12 Healthy volunteers Open, randomized two-way cross-over study of two single doses of sildenafil (oral and IV) to investigate the PK of oral and IV, including absolute bioavailability	Sildenafil IV (N = 12)	Randomized: 6 Treated: 6 Completed: 6	Sex: 6 M/0 F Mean Age: 23 yrs Race: W/B/O: 6/0/0	Two single doses of sildenafil 50 mg (**50 minute IV infusion** and two 25 mg capsules)
A148-215	6 Healthy volunteers Open PG radiolabelled study to measure the cumulative amount of drug related, radiolabelled material excreted in the urine/faeces.	Sildenafil IV (N = 3) Sildenafil oral (N = 3)	Randomized: 3 Treated: 3 Completed: 3 Randomized: 3 Treated: 3 Completed: 3	Sex: 3 M/0 F Mean Age: 51 yrs. Race: W/B/O: 3/0/0 Sex: 3 M/0 F Mean Age: 51 yrs. Race: W/B/O: 3/0/0	Single dose of 25 mg (**25 minute IV infusion**; 25 ml of 1 mg/ml solution) or 50 mg powder for oral solution
A1481024	85 adult patients with pulmonary hypertension (PH) (PAH: 45; PVH due to CHF: 34; Hypoxic PH due to COPD: 6) Single blind fourway XO dose escalation study to assess the effect of IV sildenafil on pulmonary vascular resistance in subjects with PH. TOTAL: Sildenafil IV (N = 35) Placebo (N = 10) Sildenafil IV (N = 25) Placebo (N = 9) Sildenafil IV (N = 6)	**GROUP 1a (PAH n=45)** **G1aO SIL+NO** (IV SD; Targeting concentrations: 100, 300 and 500 ng/ml) **G1aO PLA+NO** (IV SD) **G1aExt SIL+NO** (IV SD; Targeting concentrations: 10, 50 and 100 ng/ml) **G1aExt PLA+NO** (IV SD) **G1aExt. SIL alone** (IV SD; Targeting concentrations: 10, 50 and 100 ng/ml) **G1a Ext. PLA alone** (IV SD)	 Randomized: 12 Treated: 12 Completed: 7 Randomized: 3 Treated: 3 Completed: 2 Randomized: 9 Treated: 9 Completed: 9 Randomized: 3 Treated: 3 Completed: 2 Randomized: 14 Treated: 14 Completed: 10 Randomized: 4 Treated: 4 Completed: 4	 Sex: 5 M/7 F Mean Age: 55.5 yrs Race: W/B/O: 11/0/1 Sex: 2 M/1 F Mean Age: 42.7 yrs Race: W/B/O: 3/0/0 Sex: 2 M/7 F Mean Age: 55.9 yrs Race: W/B/O: 9/0/0 Sex: 0 M/3 F Mean Age: 41 yrs Race: W/B/O: 3/0/0 Sex: 1 M/13 F Mean Age: 48 yrs Race: W/B/O: 14/0/0 Sex: 2 M/2 F Mean Age: 49 yrs Race: W/B/O: 4/0/0	Series of step-wise IV infusions targeting concentrations of 100, 300, and 500 ng/ml in original study and 10, 50, and 100 ng/ml in extension phase (consisted of initial **20 minute IV infusion** followed by maintenance infusions to maintain targeted plasma concentrations)
A148-301	A single group open design study to assess safety, toleration and Haemodynamics of sildenafil in patients with IHD	Sildenafil IV (N = 8) Cumulative IV doses of 5, 10, 20 and 40mg	Randomized: 8 Treated: 8 Completed: 7	Sex: 8 M/0 F Mean Age: 60 yrs Race: W/B/O: 7/0/0 Race not documented for 1 pt	Four **15 minute infusions.** Step-wise cumulative doses of 5, 10, 20, and 40 mg **over 60 minutes**
A1481134	A randomised, DB, PG, PC, multi-centre study to assess IV sildenafil as treatment of PH post-corrected Heart surgery for congenital heart disease in children aged 0-17 yrs.	**Placebo IV** **Low IV sildenafil** Loading dose (target 40ng/ml + infusion for 24-72 hours) **Medium IV sildenafil** Loading dose (target 160ng/ml + infusion for 24-72 hours) **High IV sildenafil** Loading dose (target 320ng/ml + infusion for 24-72 hours)	Randomized: 5 Treated: 5 Completed: 4 Randomized: 4 Treated: 4 Completed: 4 Randomized: 5 Treated: 4 Completed: 3 Randomized: 4 Treated: 4 Completed: 4	Sex: 4 M/1 F Mean Age: 38.8 mo. Race: W/B/O: 3/0/2 Sex: 2 M/2 F Mean Age: 21.8 mo. Race: W/B/O: 2/0/2 Sex: 2 M/2 F Mean Age: 11.3 mo. Race: W/B/O: 2/0/2 Sex: 1 M/3 F Mean Age: 8 mo. Race: W/B/O: 3/1/0	One single dose followed by 24-72 hour infusion
A1481157	(Part1) Multicentre randomised open-label placebo controlled dose ranging study to evaluate the PK of IV sildenafil in near term and term newborns with PPHN	Sildenafil IV (Loading dose (target 150ng/ml + infusion for 48-168 hours).	Randomized: 36 Treated: 36 Completed: 31	Sex: 17 M/19 F Mean Age: 34.3 hrs. Race: W/B/O: 10/11/15	Single dose. Loading dose followed by infusion for 7 days.

PAH = Pulmonary arterial hypertension; PVH = Pulmonary venous hypertension; PH = Pulmonary hypertension; COPD = Chronic obstructive pulmonary disease; CHF = Congestive heart failure; IV = intravenous; G1aO = Group 1a Original; G1aE = Group 1a Extension; SIL = sildenafil; PLA = Placebo; NO = Nitric Oxide; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; CHF = Chronic heart failure; PPHN = (Persistent Pulmonary Hypertension of the newborn)

GCP

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

Pharmacokinetics

Pharmacokinetics (PK) was investigated in the original sildenafil male erectile dysfunction (MED) development programme (35 pharmacology studies). These studies examined the safety, tolerability,

PK, pharmacodynamics (PD), bioavailability, bioequivalence, effect of food and drug interactions of sildenafil, and PK characteristics in special patient populations.

Three Phase 1 studies were conducted during the sildenafil citrate development programme to evaluate the pharmacokinetics of IV sildenafil (studies A148-203, A148-208 and A148-215). The tables below give a summary of the pharmacokinetic variables for sildenafil and the main metabolite UK-103,320 found in these studies.

Table 4. Mean sildenafil pharmacokinetic variables in healthy volunteers after intravenous administration.

Study	Infusion Dose	N	Cmax (ng/mL)[a]	Tmax (h)[b]	AUCt (ng.h/mL)[a]	CL (L/h)[b]	Vd (L)[b]	Vss (L)[b]
148-203	20 mg in 40 mins	8	331	0.67	714	na	na	na
148-203	40 mg in 40 mins	8	833	0.58	1554	na	na	na
148-203	80 mg in 40 mins	8	1822	0.69	3711	na	na	na
148-208	50 mg in 50 mins	12	531	0.73	1289	40.8	234	104.7
148-215	25 mg in 25 mins	3	518	0.42	964	25.8	88.4	56.6

na – Not Available; N – Number of subjects.
[a] Geometric mean.
[b] Arithmetic mean.

Table 5. Mean UK-103,320 pharmacokinetic variables in healthy volunteers after intravenous administration of sildenafil

Study	Infusion Dose	N	Cmax (ng/mL)[a]	Tmax (h)[b]	AUCt (ng.h/mL)[a]
148-203	20 mg in 40 mins	8	27	1.17	119
148-203	40 mg in 40 mins	8	50	1.17	220
148-203	80 mg in 40 mins	8	124	1.33	584
148-208	50 mg in 50 mins	12	na	na	na
148-215	25 mg in 25 mins	3	38	0.83	139

na – Not Available; N – Number of subjects.
[a] Geometric mean.
[b] Arithmetic mean.

In healthy volunteers, sildenafil citrate has been given as an IV infusion ranging in dose from 20 mg in 40 mins to 80 mg in 40 mins. The mean Cmax achieved ranged from 331-1822 ng/mL, with a range in exposure (AUCt) of 714-3711 ng.h/ml. Tmax was similar for all doses studied. The pharmacokinetic variables most involved in the assessment of the dose recommendation for IV sildenafil, volume of distribution at steady state (Vss) and clearance (CL) demonstrated ranges of 57-105 l and 26-41 l/h respectively.

After i.v. administration of sildenafil a volume of distribution was found of about 105 l (study A148-208). Partitioning of sildenafil and its metabolites into erythrocytes was found in vivo, resulting in a blood-to-plasma ratio of about 1.6. In vitro studies with human plasma showed that over a concentration range from 0.01 - 10 µg/mL about 96% of sildenafil was bound to plasma proteins. Also the metabolite UK-103.320 was bound to plasma proteins for ca. 95%. No additional binding studies with specific proteins were carried out.

The pharmacokinetics of sildenafil was determined after oral administration of a solution containing 50 mg 14C-sildenafil and after an i.v. dose of 25 mg 14C-sildenafil to healthy male volunteers (study A148-215). Three volunteers received an oral solution dose of 50 mg sildenafil and 3 volunteers received 25 mg as an IV infusion in 50 mL over 25 min. Both dosage forms contained nominally 50 µCi of [14C]-labeled sildenafil.

Absorption of sildenafil after oral administration was approximately 92% whilst the oral bioavailability was 38%, this difference being due to extensive first pass metabolism. Geometric mean AUCt values indicated that sildenafil accounted for approximately 60% of the total circulating radioactivity in the plasma after IV dosing and 32% after oral dosing.

For the main metabolite of sildenafil (UK-103,320), the geometric mean Cmax value following IV dosing was 7.3% of the equivalent parameter for sildenafil. The geometric mean AUCt value was 14.4% of the equivalent parameter for the parent drug. Following oral dosing, the geometric mean Cmax value for UK-103,320 was 49% of that of the parent drug. The geometric mean AUCt value was 54% of that for sildenafil. Hence the amount of circulating metabolite was significantly lower following IV administration versus oral. The absolute bioavailability of the solution was about 38% which is in good agreement with the 41% obtained with the 50 mg capsule. The half-life of sildenafil tended to be shorter after IV administration than after oral administration, 2.18h IV vs. 3.19h, respectively.

After i.v. and oral dosing of labelled sildenafil similar radioactivity was recovered in the faeces and urine, indicating that the bioavailability is about 100%. Thus the absolute bioavailability of about 40% is due to first pass metabolism and not due to incomplete absorption.

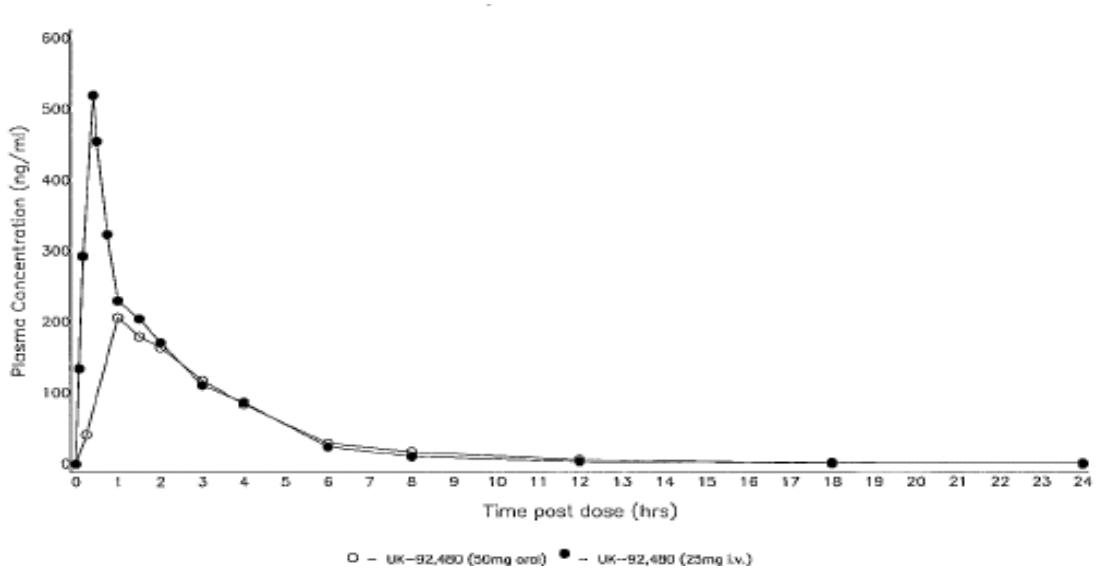


Figure 1 – Plasma concentration time-curves of sildenafil after oral administration of 50 mg and intravenous administration of 25 mg as a 25 min infusion.

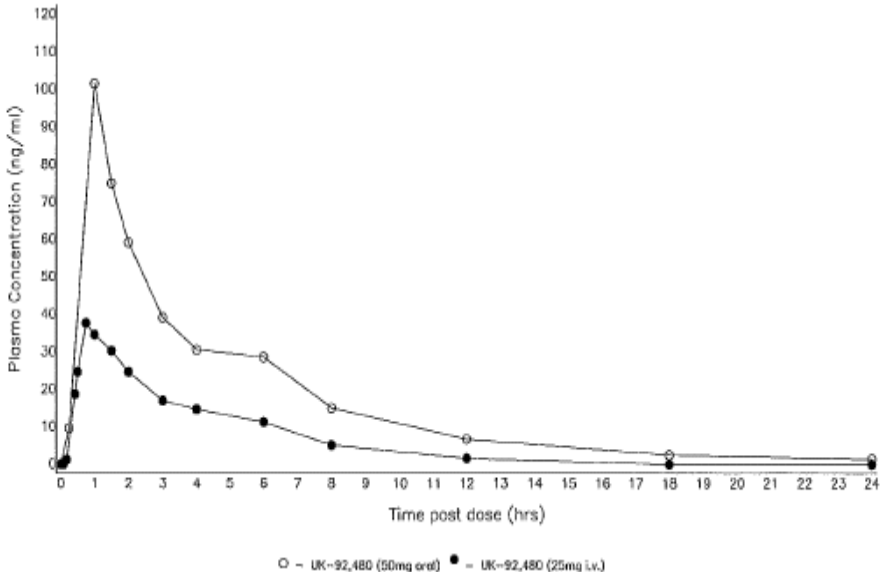
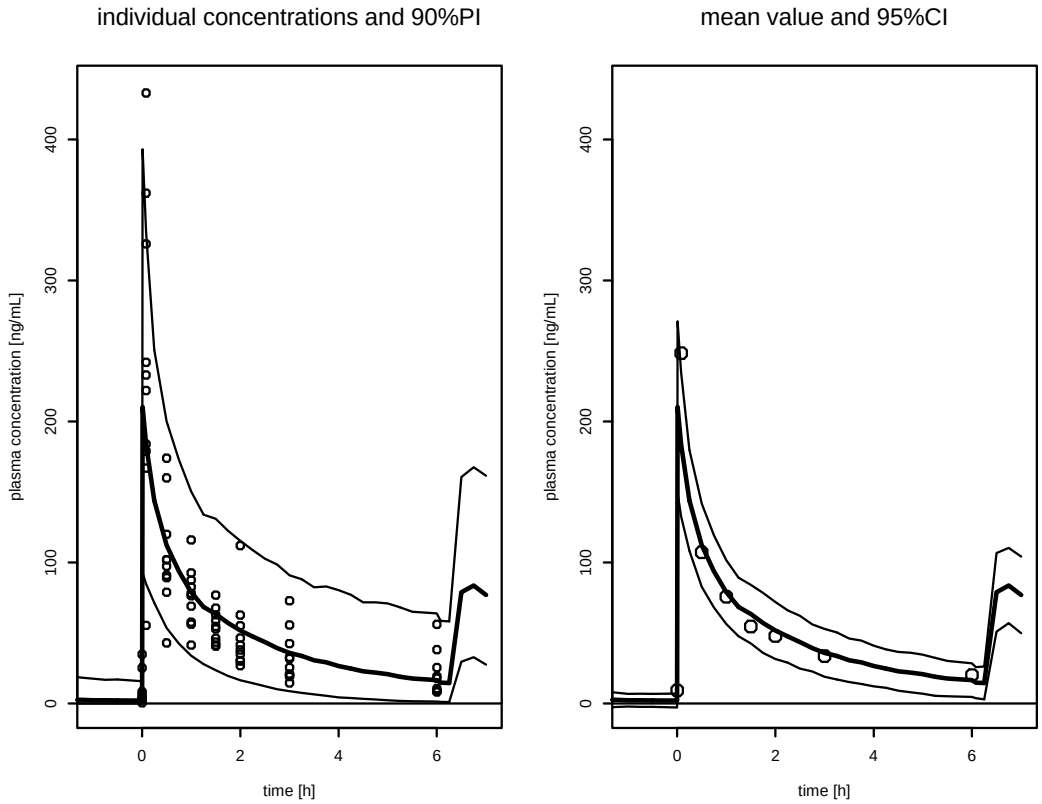


Figure 2 –Plasma concentration time-curves of UK-103,320 after oral administration of 50 mg sildenafil and intravenous administration of 25 mg sildenafil as a 25 min infusion.

The MAH provided a justification for the 10 mg intravenous dose based on calculations and simulations considering the higher total exposure following IV than the oral administration together with the relative potencies of the parent/active metabolite. However, this justification couldn't be applied to Cmax. The MAH has therefore submitted additional PK data in PAH patients receiving sildenafil administered as a bolus (study A1481262). These patients were previously on oral TID 20 mg sildenafil. The observed concentration time curves fit well within the predicted curves based on population PK modelling. The population PK model was developed based on earlier performed IV infusion, IV infusion/per os (PO) cross-over and a PO studies in healthy volunteers. The model considered the known 30% lower clearance in PAH patients and the increased clearance (estimated 2.7 times) due to co-administration of the CYP3A4 inducer bosentan.



(Bold line: simulated mean for 10 mg IV bolus for Study A1481262; Dotted lines: 90% prediction intervals; circles: The observed values in Study A1481262)

Figure 3 – The observed individual and mean values and the simulated mean and prediction intervals (PI) and confidence intervals (CI) in Study A1481262

As expected, total exposure and Cmax of parent sildenafil were higher after IV bolus administration than after oral administration of sildenafil 20 mg TID. However, total exposure and Cmax were lower than after 80 mg TID sildenafil oral administration, for which adequate long-term clinical data are available indicating that this dose is well tolerated.

Discussion on Pharmacokinetics

Drug interactions have been well characterised for use with oral Revatio at the time of the initial marketing authorisation. Theoretically, any PK drug interactions with other drugs after IV administration of sildenafil should be less than that after oral administration as there is no first pass effect.

The MAH provided an acceptable justification for the 10 mg intravenous dose based on calculations considering the higher total exposure following IV than the oral administration together with the relative potencies of the parent/active metabolite and on PK data in PAH patients receiving sildenafil administered as a bolus.

As expected, total exposure and Cmax of parent sildenafil were higher after IV bolus administration than after oral administration of sildenafil 20 mg TID. However, total exposure and Cmax were lower than after 80 mg TID sildenafil oral administration. Individual patients may experience maximal sildenafil concentrations that are in the range observed with 80 mg TID oral administration. This could be associated with individual hypotensive cases observed (see safety discussion).

Accumulation after TID oral dosing is limited. Simulation data appropriately demonstrate that no relevant accumulation is to be expected also after the intended IV bolus administration. Therefore, the lack of multiple dosing studies with an IV bolus administration is acceptable.

PK data from the study A1481024 (see clinical efficacy) are very limited because only 1 plasma level was measured at the end of each infusion step. Observed plasma levels in patients with PH after IV administration were approximately 30% higher than those predicted from healthy volunteers.

Assuming a similar exposure after 10 mg IV and 20 mg orally and as half-life tends to be shorter after IV administration than after oral administration, recommending a downward dose adjustment to 10 mg TID after a careful benefit-risk assessment and only if therapy is not well-tolerated seem to be appropriate. No specific data for IV sildenafil are available in patients with hepatic impairment. Oral sildenafil is subject to an important first-pass metabolism, theoretically resulting in higher exposure than after IV administration at "proportional" doses (20 mg oral vs. 10 mg IV). Therefore, recommending a downward dose adjustment to 10 mg TID after a careful benefit-risk assessment and only if therapy is not well-tolerated seem to be appropriate.

Clinical efficacy

Revatio 0.8 mg/ml solution for injection is intended for use in haemodynamically stable PAH patients who are currently undergoing treatment with oral Revatio but who are temporarily unable to take or tolerate oral medications. As such, the indicated population for Revatio IV is identical to that for oral Revatio. Since use of Revatio IV will involve the administration of the same therapeutic exposure to the same active ingredient in the same clinical population for treatment of the same medical condition, the MAH considered that there is no rationale for the expectation of a difference in efficacy following intravenous administration of Revatio.

No new clinical studies were submitted. To support the efficacy of the IV formulation and the need for continuous treatment, the MAH referred to 2 clinical studies submitted in the initial marketing authorisation application, Study A1481024 and Study A1481141, respectively.

Study	**Patient population number of patients**	**Dose**	**Study design**
Phase 2A A1481024	PH (N = 85) - PAH (N = 45) - PVH due to CHF (N = 34) - Hypoxic PH due to COPD (N = 6)	 Sildenafil IV (N = 35) Placebo (N = 10) Sildenafil IV (N = 25) Placebo (N = 9) Sildenafil IV (N = 6)	Series of step-wise IV infusions targeting concentrations of 100, 300, and 500 ng/ml in original study and 10, 50, and 100 ng/ml in extension phase (consisted of initial infusion followed by maintenance infusions to maintain plasma concentration). Hemodynamic measures
Phase 3 A1481141	PAH: Placebo (N=106) Sildenafil (N=134)	Optimized oral sildenafil dose of 20, 40 or 80mg TID	PAH patients stabilized on epoprostenol were randomized to receive placebo or oral sildenafil and evaluated at week 16 by 6-MWT and clinical worsening.

Study A1481024

Design
This was a multi-centre trial to assess the safety, efficacy and toleration of intravenous (IV) sildenafil in subjects with pulmonary hypertension. Patients were stratified into 1 of 3 groups prior to randomisation according to type of pulmonary hypertension (pulmonary arterial hypertension [primary and secondary] [Group 1a], pulmonary venous hypertension due to congestive heart failure [Group 1b], and hypoxic pulmonary hypertension [Group 2]). (Only results of group 1a were presented and assessed in this application).

Objectives
The primary objective was to assess the effect of intravenous (IV) sildenafil on some hemodynamic parameters in adults with pulmonary hypertension.

Drug administration
A series of step-wise IV infusions were administered targeting concentrations of 100, 300, and 500 ng/ml in the 'original study' and 10, 50, and 100ng/ml in the 'extension phase'. Patients with PAH (group1a) subjects were randomised to receive either sildenafil or placebo (ratio 3:1). After the initial baseline assessment (Baseline 1) the indicated patients were administered 40ppm of NO by inhalation for five minutes. When the value of pulmonary arterial pressure (PAP) returned to a re-established baseline (Baseline 2) (± 5% Baseline 1) haemodynamic measurements were conducted followed by the step infusion of study drug. The infusion was administered at a controlled rate to maintain plasma concentrations of 100, 300 and 500ng/ml consequtively in the original part of the protocol.
The haemodynamic measurements at each plasma level were performed after 10 minutes of every maintainance step of the infusion.

Results
The following tables summarize the main results of study A1481024. Table 6 shows the patient distribution. Other tables below summarize the results of PVR and PAP in group 1a pulmonary arterial hypertension.

Table 6. Group 1a: Pulmonary arterial hypertension

	Original		Extension			
	Sildenafil with NO	Placebo with NO	Sildenafil with NO	Placebo with NO	Sildenafil without NO	Placebo without NO
Entered Study	12	3	9	3	14	4
Completed study	7	2	9	2	10	4
Evaluated for PK	12	0	9	0	14	0
Evaluated for efficacy (ITT)	12	3	9	3	14	4
Assessed for adverse events	12	3	9	3	14	4
Assessed for laboratory data	9	3	9	3	13	3

Table 7. Mean±SE absolute PVR (dyne.sec/cm^5), subjects with NO (original phase).

Treatment	**Baseline 1 N= 10**	**During NO N= 10**	**Post NO N=3**	**Baseline 2 N= 10**	**100 ng/ml N= 10**	**300 ng/ml N= 9**	**500 ng/ml N= 6**
Sildenafil	932.34 140.9	860.08 145.6	1077.67 462.9	954.94 145.4	736.89 113.8	788.23 120.6	770.70 140.9

Table 8. Mean±SE absolute PVR (dyne.sec/cm^5), subjects with NO (extension phase).

Treatment	**Baseline 1 N= 9**	**During NO N= 9**	**Post NO N=9**	**Baseline 2 N= 9**	**100 ng/ml N= 9**	**300 ng/ml N= 9**	**500 ng/ml N= 9**
Sildenafil	1116.87 199.8	912.25 189.7	1125.51 192.1	1148.78 229.0	1031.85 178.9	942.25 167.4	864.70 160.4

Table 9. Mean±SE absolute PVR (dyne.sec/cm^5), subjects without NO (extension phase).

Treatment	Baseline 1 N= 7	Baseline 2 N= 10	10 ng/ml N= 14	50 ng/ml N= 12	100 ng/ml N= 11
Sildenafil	774.74 125.2	1140.37 168.8	899.68 117.0	832.57 108.7	778.43 118.5

Table 10. Mean±SE absolute PAP (mmHg), subjects with NO (original phase).

Treatment	Baseline 1 N= 12	During NO N= 12	Post NO N=4	Baseline 2 N= 12	100 ng/ml N= 12	300 ng/ml N= 11	500 ng/ml N= 7
Sildenafil	45.60 3.5	43.79 4.1	42.30 6.6	45.04 3.5	39.58 3.8	40.93 3.5	38.29 4.3

Table 11. Mean±SE absolute PAP (mmHg), subjects with NO (extension phase).

Treatment	Baseline 1 N= 9	During NO N= 9	Post NO N=9	Baseline 2 N= 9	10 ng/ml N= 9	50 ng/ml N= 9	100 ng/ml N= 9
Sildenafil	50.22 4.0	44.00 3.7	49.33 3.4	49.56 3.9	46.89 3.3	44.44 3.1	43.22 3.2

Table 12. Mean±SE absolute PAP (mmHg), subjects without NO (extension phase).

Treatment	Baseline 1 N= 7	Baseline 2 N= 10	10 ng/ml N= 14	50 ng/ml N= 12	100 ng/ml N= 11
Sildenafil	47.00 3.9	59.00 4.6	53.36 3.2	48.25 3.3	46.55 3.7

Although (i) the sample size in Study A1481024 was small, (ii) there is a known inter-subject variation in haemodynamic response and (iii) there is an unknown relationship between haemodynamic response and clinical outcome, the consistency of response in Study A1481024 with that seen in the pivotal oral study, A1481140, is supportive of the efficacious treatment of key haemodynamic parameters following administration of IV sildenafil citrate in patients with pulmonary hypertension, including PAH.

Study A1481141

Design

This was a multinational, multi-centre, randomised, double-blind, placebo controlled, parallel group study. Eligible subjects were randomised to receive a subject optimised dose of sildenafil (20, 40 or 80mg TID) plus epoprostenol or placebo TID plus epoprostenol in a 1:1 ratio. A total of 230 evaluable subjects were planned in the protocol (115 per treatment group). The study comprised a screening visit, a 16-Week treatment period with visits at baseline, Weeks 4, 8, 12 and 16, and a follow-up visit 30 to 40 days after the last dose of study medication.

Subjects aged ≥18 years with primary PAH or PAH associated with connective tissue disease (CTD) or PAH associated with surgical repair were included. Subjects had to have been on epoprostenol for at least 3 months, and been on an estabilised, "optimal" dose for at least 4 weeks before randomisation. Subjects had to have a mean pulmonary artery pressure (mPAP) ≥25mmHg and a pulmonary capillary wedge pressure (PCWP) ≤15mmHg at rest via right heart catheterisation within 21 days before randomisation, and a baseline 6-Minute Walk test distance ≥100m and ≤450m.

Drug Administration

Subjects randomised to sildenafil initially received sildenafil 20mg TID for 4 weeks. At the Week 4 visit, they were up-titrated to 40mg TID for 4 weeks, and at the Week 8 visit they were up-titrated to 80mg TID for 8 weeks. Subjects randomised to placebo underwent dummy up-titration at Weeks 4 and 8.

Efficacy Evaluations
The primary efficacy endpoint was the change from baseline at Week 16 in the total distance walked during the 6-Minute Walk test. The secondary efficacy endpoints were the change from baseline at Week 16 in mean pulmonary artery pressure (mPAP) and BORG dyspnoea score, and the time to clinical worsening. The tertiary endpoints were the change from baseline at Week 16 in haemodynamic parameters and WHO Functional Class.

Three post-hoc analyses were performed on the efficacy data, the relevant one to the current submission is presented here. Time to clinical worsening while on sildenafil 20mg was assessed post-hoc by recording clinical worsening events up to the day of the Week 4 visit. It was from this day that sildenafil subjects were up-titrated from 20mg to 40mg (and placebo subjects underwent dummy up-titration). If no event occurred time to event was censored from the day of the Week 4 visit.

Results (Only results of the post-hoc analysis were presented)
An improvement was seen as early as the Week 4 visit, at which point there is a significant (p = 0.0256) difference between subjects on sildenafil 20 mg TID compared to placebo on the clinical worsening endpoint (Table 13). The Kaplan-Meier curves (Figure 4) show an early separation of the two treatments. This would suggest that the improvements in the time to clinical worsening are already evident whilst the subjects are on the 20 mg dose. Although it is not known how many doses of sildenafil can be missed before having an impact on time to clinical worsening current knowledge of the progressive nature of PAH suggests that treatment should be continuous. Accordingly, the availability of an IV formulation that provides similar plasma exposure to 20 mg TID doses of sildenafil provides a further treatment option for physicians.

Table 13. Summary of Clinical Worsening: Events Occurring Up To and Including the Day of Week 4 -

Reason for Clinical Worsening	Placebo (N=131)		Sildenafil (N=134)	
Worsening* (N(%))	9	(6.9)	2	(1.5)
Death	3	(2.3)	0	(0.0)
Lung Transplantation	0	(0.0)	0	(0.0)
Hospitalisation due to Pulmonary Hypertension	4	(3.1)	2	(1.5)
Change in Dose of Epoprostenol Therapy due to Clinical Deterioration	5	(3.8)	0	(0.0)
Initiation of Bosentan Therapy	0	(0.0)	0	(0.0)

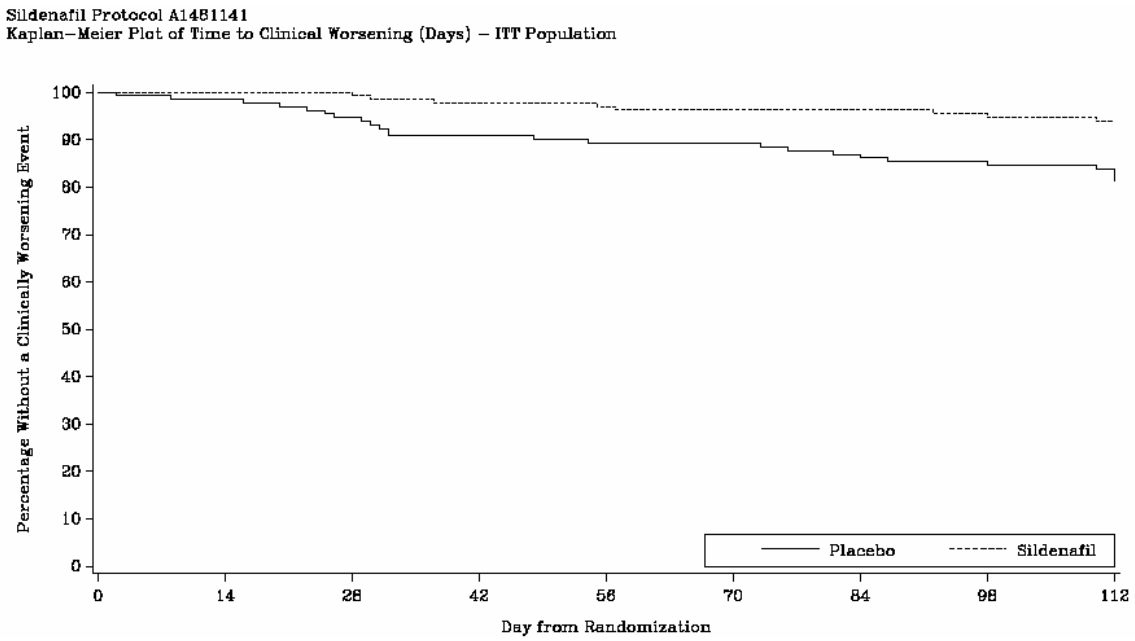


Figure 4 –Kaplan-Meier Plot of the time to clinical worsening (days) – Study A1481141

Discussion on clinical efficacy

No new efficacy studies were submitted in this application. The rationale of the MAH is acceptable as no need is foreseen to demonstrate efficacy separately for the intravenous formulation, considering that the efficacy of Revatio continuous oral administration is already established and provided equivalent doses are given. The dose of 10 mg IV bolus was calculated taking into consideration the higher sildenafil but lower metabolite exposure following IV administration and the relative potencies of both, which can be acceptable.

Study A1481024 was presented in the initial marketing authorisation application as part of the pharmacodynamic program. The results of this study demonstrated a positive hemodynamic effect for Revatio on the pulmonary vasculature. Maximum reductions in the relevant pulmonary parameters pulmonary vascular resistance PVR and pulmonary artery pressure mPAP appeared to be reached at plasma sildenafil concentrations of 100 ng/ml, while only limited reductions in mean systemic blood pressure BP were observed at concentrations below 100 ng/ml in patients without NO. This study indicated that plasma levels up to 100 ng/ml sildenafil appear to be an appropriate target with relative selectivity to the pulmonary circulation. Based on the PK study 148-207 (original Revatio submission), the mean maximum exposure at steady state of sildenafil following 20 mg TID was calculated to be 113 ng/ml and accordingly this dose was considered clinically relevant for further investigation in the pivotal study A1481140 (40 and 80 mg TID was also investigated). The results of the pivotal study showed a significant effect for sildenafil 20 mg TID on exercise capacity. This efficacy can in turn be extrapolated to the IV administration as comparability in other PK parameters are currently shown.

In order to emphasize the need for a maintained drug level, the MAH presented a post-hoc analysis from study A1481141. Time to clinical worsening between placebo and sildenafil 20 mg was assessed by recording clinical worsening events up to the day of the Week 4 visit. An improvement was seen as early as the Week 4 visit, at which point there is a significant ($p = 0.0256$) difference between subjects on sildenafil 20 mg TID compared to placebo. The data should be regarded cautiously considering the post hoc nature of the analysis. Still, it can be agreed with the MAH that there appears to be some benefit as early as 4 weeks on the registered dose of 20 mg TID sildenafil compared to placebo suggesting the need for continuous administration. Although no robust clinical evidence is presented to demonstrate actual deterioration in the patients' conditions with temporary drug interruptions, it can be agreed that generally maintenance of adequate blood levels is a rational goal. Accordingly, the need to develop an IV formulation is acknowledged.

Clinical safety

The MAH provided safety data from the seven clinical studies as well as post marketing data and a literature review. Originally, the clinical development program for Revatio IV did not include any data regarding Sildenafil 10 mg bolus IV administration.

At the request of the CHMP, in order to adequately assess the safety of the IV bolus administration, the MAH submitted the results of study A1481262. This was a single-centre, single dose (10 mg Revatio IV bolus), open-label safety and pharmacokinetic study. A total of 12 PAH subjects, already stable on oral Revatio 20 mg TID, were planned to complete the study. However, after recruiting 10 subjects and analyzing their safety data, the company took a " pragmatic" decision and stopped recruitment as it was considered unlikely that their results would impact the general conclusions of the study. This approach would have been acceptable if the recruited numbers were large enough to allow for robust conclusion, which is not the case as will be shown below. The study design was considered acceptable.

The actual diagnosis of most of the patients was not mentioned (one patient was listed with idiopathic PAH, while the other patients had a general diagnosis of PAH), nor their WHO function class. However, 8/10 patients were on bosentan in addition to Revatio, signifying that they are possibly in severer stages necessitating combination therapy. The results of the 10 patients showed that the administration of Revatio 10 mg bolus IV injection resulted in a maximum mean reduction of -9.4 ±

11.66 mmHg and -3.0±4.93 mmHg in sitting SBP and DBP at 0.5 hours and 1 hour post dose respectively. Maximum mean reduction of -6.1 ± 11.91 mmHg and -4.3 ± 6.29 mmHg standing SBP and DBP were recorded at 0.5 hour compared to pre-dose levels.

Table 14. Changes from baseline in Systolic (sitting, standing and postural) and Diastolic (sitting, standing and postural)

Time (HOURS)		Systolic			Diastolic		
		Sitting	Standing	Posturnal	Sitting	Standing	Postural
Pre-dose	N	10	10	10	10	10	10
	Mean	120.1	118.4	1.7	69.6	68.6	0.3
	Std. Dev.	17.08	17.54	9.25	12.16	9.44	10.90
	Median	129.0	120.5	3.3	75.0	69.8	-2.8
	Min	95	94	-10	42	53	-12
	Max	138	146	18	82	86	29
0.5	N	10	9	9	10	9	9
	Mean	-8.4	-6.1	-0.8	-2.6	-4.3	-2.9
	Std. Dev.	11.66	11.81	14.10	7.31	6.29	4.35
	Median	-8.0	-2.5	-2.0	-3.5	-2.0	-2.0
	Min	-33	-29	-27	-11	-16	-13
	Max	10	8	14	16	4	1
1	N	10	10	10	10	10	10
	Mean	-9.1	-0.1	-7.3	-3.0	0.4	-0.4
	Std. Dev.	12.53	12.50	14.12	4.93	6.93	21.08
	Median	-8.0	0.8	-2.8	-3.8	-0.3	-6.0
	Min	-35	-21	-43	-13	-10	-16
	Max	12	20	5	4	12	58
2	N	10	9	9	10	9	9
	Mean	-3.8	-2.8	0.0	-0.9	-0.4	-4.1
	Std. Dev.	9.32	12.21	12.27	4.72	3.63	5.34
	Median	-1.3	-4.0	4.5	-0.8	0.0	-2.0
	Min	-21	-19	-28	-9	-6	-15
	Max	12	17	14	6	5	2
3	N	10	10	10	10	10	10
	Mean	-6.1	-1.2	-3.2	-2.2	-0.9	-4.9
	Std. Dev.	4.93	10.23	11.16	3.88	5.24	3.59
	Median	-4.0	-0.3	1.0	-3.3	-1.0	-4.5
	Min	-14	-16	-21	-6	-12	-11
	Max	2	14	12	7	9	1
6	N	10	10	10	10	10	10
	Mean	1.3	2.5	0.5	1.1	2.3	-1.2
	Std. Dev.	6.15	11.60	12.76	6.70	6.96	11.03
	Median	1.0	2.5	1.3	1.3	2.8	-3.5
	Min	-7	-21	-26	-9	-11	-11
	Max	12	19	21	14	11	29

This was accompanied by only 3 mild AEs related to the drug. In one patient, a change of the SBP of ≥30 mmHg was recorded. As the patient was originally hypertensive and this hypotension was not accompanied by symptoms e.g postural hypotension or syncope, the MAH considered that the case would not fall into the category of excessive vasodilation. This explanation appeared plausible.

The results are reassuring, but it is difficult to draw robust conclusions to the safety of Revatio IV bolus administration as the number of recruited patients was too few and the high Cmax may be correlated to more severe BP lowering effects as seen in one patient. According to the MAH, no abnormal ECG tracings were recorded.

The MAH also provided safety data from Revatio IV infusion in patients with PH (study: A1481024) ischemic heart disease patients (Study: 148301), post-operative PH pediatric patients (A1481134) or PPHN patients (A1481157) or healthy volunteer studies (Studies: 148203-148208 and 148215).

The most relevant of these safety data are considered to originate from study A1481024. A subgroup of 35 PAH is the focus of this report. In study A1481024, sildenafil was administered in 35 PAH patients (other subtypes of PH recruited in this study are not described in the current assessment) as a series of step-wise IV infusions targeting 300 ng and 500 ng/ml in the original study and 10, 50 and 100 ng/ml in the extension phase.
The reported adverse events were generally comparable to the adverse events reported to the pivotal study A1481140 where sildenafil was orally administered, although the number of events are too few

to allow for proper conclusions. The relation of the reported AE to the plasma concentration was not reported. None of the reported serious adverse events or the one case of death were considered treatment related. Regarding systemic blood pressure measurements, as could be expected, the administered Sildenafil IV infusions appear to have resulted in systemic reductions in blood pressure. These were generally tolerated, however, in some cases this led to study discontinuation (1 case reported as AE; 6 other cases because of protocol definitions).

Based on the whole A1481024 population, no clinically significant laboratory findings were noticed. Two cases of discontinuations due to adverse events related to sildenafil administration were reported in the PAH subgroup, one case of nausea and one case of hypotension. In the reported case of hypotension, no clinical symptoms as a result of the drop in systemic pressure were observed. The severity was considered mild, and no action other than stopping the sildenafil infusion was taken. The safety results of study A1481024 generally support that Sildenafil IV infusions achieving plasma levels up to 500 ng/ml were well tolerated. This is reassuring considering that the predicted upper 90% CI of Cmax for the commercial 10 mg IV bolus is not expected to exceed 300 ng/mL.

In patients with stable ischemic heart diseases (study 148301), doses of Sildenafil 40 mg IV infusion appeared to be well tolerated, though the numbers (n=8) are too few to allow for any robust conclusions.

The reported cases (n=3) in the post marketing experience involve un-registered use of Sildenafil (2 cases of paediatric use and one case dissolving Viagra tablets and injecting them). For the compassionate use, no details were supplied by the MAH precluding any assessment.

In the three healthy volunteer studies A148-203, A148-208 and A148-215 (n= 23), the administered doses varied between 20 mg to 80 mg Sildenafil IV infusion. Generally, the reported adverse events following IV infusion were comparable to those reported after oral administration, mostly related to vasodilation.

The MAH submitted data from the paediatric studies A1481134 and A1481157 in which pulmonary hypertension paediatric patients were administered sildenafil IV during the post-operative period after corrective cardiac surgery or Persistent Pulmonary Hypertension of Neonates PPHN patients, respectively. As Sildenafil is not authorised for paediatric use and the administered dose is accordingly not properly assessed, the submitted information was not considered relevant to this application.

The MAH also presented a literature review including 10 clinical studies spanning many indications, patient populations and dose ranges. The majority of the studies used short infusions ranging from 0.025 mg/kg over 10 minutes to 0.3 mg/kg/min for 14 days in infants and 300 mcg over 6 minutes to 60 mg over an hour in adults. No special safety issues were specifically identified, but no conclusions can be made considering the different route of administration. The study of Alp et al. (2006) deserves special attention as it is the only study in which sildenafil was administered as an IV bolus. A dose of 12.5 mg followed by 37.5 mg was administered in 6 PH patients secondary to COPD. The dose was well tolerated and the pulmonary vascular resistance PVR was more markedly reduced than the systemic vascular resistance SVR even after 12 hours of administration. The results are generally supportive considering that the administered dose is 5 times the currently recommended dose.

Discussion on clinical safety

The anticipated safety issues from the bolus injection of a vasodilator drug are mainly related to hypotension. Results of study A1481262 did not identify serious safety issues following the administration of Revatio IV 10 mg bolus dose in the 10 patients studied. However, the safety database is too limited to allow robust conclusions. The MAH will introduce a targeted pharmacovigilance surveillance programme to capture events of hypotension and associated problems. In addition, Line listing for IV patients will be provided every 6 months and a PSUR as per the normal schedule. If warranted, new safety information from the line listings may trigger the restart of the regular PSUR periodicity.

The CHMP was concerned about the proposed vial size of 40 mg in 50 ml, when the recommended dose per administration is 10 mg with each administration requiring a new vial, as this would be a potential for medication errors. The MAH committed to develop a 20 ml presentation containing a nominal fill volume of 12.5 ml (10 mg) by May 2010. Until this new presentation is available, a controlled distribution system and an educational program are proposed to alert the health professionals about the potential risk related to the vial size.

1.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

A pharmacovigilance system document (version 2.0) has recently been submitted and assessed (EMEA/H/C/638/II/23, Commission Decision on 3 August 2009), and it is concluded that the pharmacovigilance system as described by the MAH is of good quality and is in line with section 2.2 of the Volume 9A of "The Rules Governing Medicinal Products in the European Union".

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAH submitted a new version of the Risk Management Plan (RMP), which includes updated sections related to this new application for intravenous administration. This RMP included a risk minimisation plan.

As indicated in the discussion above, the current safety data cannot substitute the need to exclude safety issues mainly related to vasodilatation following the bolus administration. A targeted pharmovigilance programme should be agreed before launch to that effect.

In addition, Revatio 0.8 mg/ml solution for injection will be available as a clear solution for injection in a 50 ml single use vial containing 40 mg of sildenafil (i.e. 0.8mg/ml). The recommended dose is 10mg (corresponding to 12.5 ml), administered three times a day. The vial should not be used as a multidose product since there is no preservative in the formulation. After each intravenous administration, the non-utilized content of the vial should be discarded with the vial.

Therefore, until a 20 ml presentation containing a nominal fill volume of 12.5 ml (10 mg) is available, there is the potential for medication errors, through the use of doses greater than the recommended dose being administered to patients, and through the potential for a single vial to be used more than once for the same or different recipients. It was therefore agreed that additional risk minimisation activities (controlled distribution system and educational pack) would be implemented to that effect.

A summary of the agreed version 4.2 of the RMP is provided in the table below:

Table 15. Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Epistaxis/ Bleeding events	Enhanced Pharmacovigilance (Data Capture Aid) Data from ongoing Clinical Studies PSUR	Information in Section 4.4 of the SPC
Risk related to anti-platelet effects of sildenafil in the presence of a NO donor	Enhanced Pharmacovigilance (Data Capture Aid)	Contraindication in Section 4.3 of the SPC

	PSUR	
Long-term CV safety data	Enhanced Pharmacovigilance (Data Capture Aid) Data from ongoing Clinical Studies PSUR	Information in Section 4.3 of the SPC
Hypotension	Enhanced Pharmacovigilance (Data Capture Aid) Data from ongoing Clinical Studies Revatio Hypotension Pharmacovigilance Monitoring Programme for IV Revatio patients	Information in Section 4.3 of the SPC Educational programme for Health Care providers
Long term mortality data	Mortality data provided by ongoing open-label clinical studies and their long-term clinical follow-ups.	Information in Section 5.1 of the SPC
Long-term ocular safety data	Enhanced Pharmacovigilance (Data Capture Aid) Data from ongoing Clinical Studies PSUR	-
A risk of NAION in PAH population is unknown	Enhanced Pharmacovigilance (Data Capture Aid) Data from ongoing Clinical Studies PSUR	Contraindication in Section 4.3 of the SPC
Medication error for the Revatio Solution for injection 50 ml vial	Appropriate and clear instructions in labeling, patient information leaflets, packaging of the vial and on the vial itself. Revatio Solution for Injection 50 ml hypotension Pharmacovigilance Monitoring Programme Provision of 6monthly IV listings and yearly Revatio PSURs	Following discussions with the Agency, the MAH has undertaken, as a post approval commitment, to apply for a 20 ml vial presentation containing a nominal fill volume of 12.5 ml (10 mg). This MAH commits to filing a variation for the smaller vial no later than May 2010. Controlled Distribution of the 50 ml vial. Educational programme for Health Care providers
Safety data is missing in PAH patients co-prescribed sildenafil with approved therapies: iloprost or bosentan	Data from ongoing and planned Clinical Studies Characterization of sildenafil iloprost users study	-
Data is limited in paediatric population	Data from ongoing Clinical Studies	Information on Section 4.2 of the SPC

Data is limited in pregnant women	Enhanced Pharmacovigilance (Data Capture Aid) PSUR	Information in Section 4.6 of the SPC
Data is limited in patients with severe renal impairment	Enhanced Pharmacovigilance (Data Capture Aid)	Information in Section 4.2 of the SPC

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

1.6 Overall conclusions, risk/benefit assessment and recommendation

Revatio 0.8 mg/ml solution for injection was proposed for PAH patients who may find themselves in clinical settings where they are temporarily unable to take oral medications or unable to absorb medications enterally. Although no robust clinical evidence is presented to demonstrate actual deterioration in the patients' conditions with temporary drug interruptions, it can be agreed that maintenance of adequate blood levels is a rational goal. Accordingly, the need to develop an IV formulation is acknowledged.

The quality of the solution for injection has been adequately described. The excipients used in the preparation of the product and the manufacturing process selected are appropriate. The drug product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in clinic.

At the time of the CHMP opinion, there were some minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking and committed to resolve these issues as Follow-Up Measures after the opinion, within an agreed timeframe.

No new efficacy studies were submitted in this application. This is acceptable as no need is foreseen to demonstrate efficacy separately for the intravenous formulation as the efficacy of Revatio for oral administration is already established provided equivalent doses are given. The need to maintain therapeutic drug concentrations is also rational. Based on the submitted PK data, the proposed dose of 10 mg IV bolus is acceptable.

Limited safety data specific to sildenafil 10 mg IV bolus dose is currently available. No serious safety concerns were identified, though the numbers are too limited to allow robust conclusions. Supportive data from sildenafil IV infusion administration was also submitted. Doses of 20 to 80 mg sildenafil IV infusion appear to have been well tolerated.

The proposed vial size is of concern as this would be a potential for medication errors. The MAH committed to develop a 20 ml presentation containing a nominal fill volume of 12.5 ml (10 mg) by May 2010. Until this new presentation is available, a controlled distribution system and an educational program are proposed to alert the health professionals about the potential risk related to the vial size.

In summary, there may be a need to develop a parenteral route of administration, to ensure continuous adequate levels of sildenafil in cases when oral intake is not possible or inadequate. Efficacy following sildenafil IV bolus administration is expected to be comparable to that following oral administration. Safety data do not identify serious adverse events associated with this IV bolus administration, though the data is too limited. A targeted pharmacovigilance surveillance programme to capture events of hypotension and associated problems will be introduced.

The MAH conducted a user consultation for the package leaflet of the Revatio 0.8 mg/ml solution for injection. The Readability has been tested adequately.

Changes related to the QRD review of the Revatio 0.8 mg/ml solution for injection product information were also implemented to the Revatio 20 mg film-coated tablets, where applicable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Revatio 0.8mg/ml solution for injection, for the *treatment of patients with pulmonary arterial hypertension who are currently prescribed oral Revatio and who are temporarily unable to take oral medicine, but are otherwise clinically and haemodynamically stable. Revatio (oral) is indicated for treatment of 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,*
was favourable and therefore recommended the granting of the marketing authorisation of this new strength, new pharmaceutical form and new route of administration.