SCIENTIFIC DISCUSSION

1. Introduction

Revatio 20 mg film-coated tablet is indicated for the 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. The active substance is sildenafil. The recommended dose is 20 mg three times a day.

PAH is a disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in a progressive increase in pulmonary arterial resistance and, ultimately, right ventricular failure and death. PAH is defined by right-heart catheterization showing a precapillary pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg with exercise, with a pulmonary artery wedge pressure < 15 mmHg). There is a female-to-male preponderance (1.7:1), with patients most commonly presenting in the third and fourth decades, although the age range is from infancy to greater than 60 years. A diagnosis for primary (or idiopathic) pulmonary hypertension is made when no known risk factor is identified. Baseline NYHA functional classification is a strong predictor of survival. The functional classification of PAH is as follows:

- Class I: PAH without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class II: PAH resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class III: PAH resulting a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class IV: PAH resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

As a general measure, patients with PAH are encouraged to engage in activities appropriate to their physical capabilities in order to prevent deconditioning and attendant worsening of overall function. No current treatment cures this rare, devastating condition. However, during the past treatment options for patients with the disease have evolved to help prolong their survival and improve their quality of life. Currently, conventional treatment for patients with primary and secondary PAH includes calcium-channel blockers, diuretics, anticoagulants and oxygen. In addition, an endothelin-1 receptor antagonist (bosentan), an intravenous prostacyclin (epoprostenol) and an inhaled prostacyclin (iloprost) have also been authorised for the treatment of PAH in various European countries. As a last resort, a lung or heart/lung transplant may be offered to the patient.

Sildenafil is an orally-active, potent and selective inhibitor of the enzyme phosphodiesterase 5 (PDE5), that causes the breakdown of cyclic guanosine monophosphate (cGMP). Given the high levels of PDE5 in the pulmonary endothelium, and the role of the nitric oxide (NO)/cGMP system in modulating pulmonary vascular tone, sildenafil has been studied in PAH. In patients with PAH, inhibition of PDE5 could lead to selective (NO/cGMP-dependent) vasodilatation of the pulmonary vascular bed (with a lesser degree of vasodilatation in the systemic circulation), resulting in reduced pulmonary arterial pressure and symptomatic improvement.

Sildenafil is also the active substance of Viagra which has previously been authorised through the Centralised Procedure for the treatment of male erectile dysfunction (MED). The recommended dose for the treatment of MED is 50 mg and may be increased to 100 mg or decreased to 25 mg, with a maximum recommended dosing frequency of once per day.

2. Part II: Chemical, pharmaceutical and biological aspects

Quality aspects

Sildenafil citrate is currently marketed in the EU as Viagra film coated tablets (25, 50 or 100 mg) (EMEA/H/C/202). The EU marketing authorization for Viagra was approved on 14 September 1998. The chemistry, manufacturing and control (CMC) information described in the Drug Substance section of Quality Module 3 of this dossier encompasses the original Viagra file as well as the subsequent approved variations until March 2004, reformatted in Common Technical Document (CTD) format.

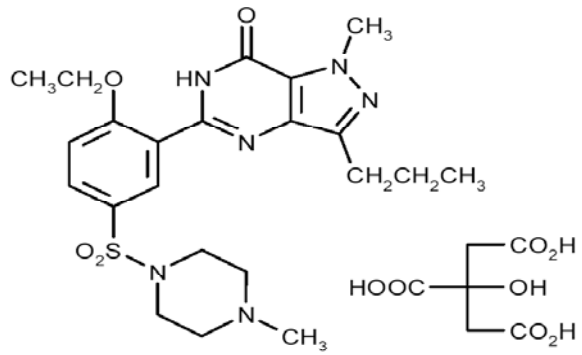
Introduction

Revatio is presented as a white, round, biconvex film-coated tablets containing 20 mg of sildenafil (as citrate salt) as active substance. Other ingredients are cellulose microcrystalline, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate. The film tablet coat contains Opadry white (hypromellose, titanium dioxide, lactose monohydrate and glycerol triacetate) and Opadry clear (hypromellose and glycerol triacetate).

The tablets are packed in PVC blister sealed with aluminium foil.

Drug Substance (to be changed in the EPAR to "Active Substance")

Sildenafil citrate has the chemical name 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]-4-methylpiperazine citrate, and the structural formula is the following:



Sildenafil citrate is a crystalline, white to off white monomorphic solid. The solubility of sildenafil citrate in water has been determined as being 3.5 mg/ml, at 23°C. Solubility determinations in various buffers showed a maximum solubility of approximately 24 mg/mL at pH 2.0. The intrinsic dissolution rate has been found to be 0.2 mg/min/cm^2 in water and 0.7 mg/min/cm^2 in 0.01M HCl. Sufficient information was provided on physical form, solubility, ionisation constant, thermal properties, hygroscopicity and polymorphism. There are no structural isomers of sildenafil citrate and no polymorphs have been found of anhydrous sildenafil citrate. A new form of a citrate salt of sildenafil has been observed during recent solubility studies of sildenafil citrate at 4ºC. This form has been characterized as a hydrated form of sildenafil hemi-citrate. It has been demonstrated that the sildenafil hemi-citrate hydrate form is not produced under conditions employed during the commercial manufacturing process for either the sildenafil citrate (anhydrous) drug substance or the drug product and that the different stoichiometry of the hemi-citrate hydrate prevents its formation during storage of either the drug substance or the drug product.

- Manufacture

Sildenafil citrate is synthesised in three steps. Optional purification procedures are described in order to ensure the quality of the isolated intermediates. Sildenafil citrate, the finished product, may be purified. The dry product is sieved or milled if necessary to meet the particle size acceptance criteria.
Adequate information on the starting materials and reagents and solvents were provided, including specifications, methods and where relevant also validations. Specifications have been set for the intermediate products, starting materials and reagents. The impurities are discussed. Methods and where relevant validations have been provided
Batch analysis data produced with the proposed synthetic route provided show that the active substance can be manufactured reproducibly.

- Specification

The active substance specifications includes tests for appearance, particle size, identification (IR, HPTLC), assay (HPLC, 98-102%), purity, residual solvents, water, sulphated ash and heavy metals.

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Certificates of analysis issued by the finished product manufacturer are provided. The results comply with the specifications.

- Stability

The stability parameters tested on the drug substance are assay, impurities, appearance and water content. Data are provided for four batches of sildenafil citrate stored at 25°C/60% RH and 30°C/60%RH (both 5 years) and 40°C/75% RH (6 months). In addition, results from a photostability study are presented

All the above-mentioned studies demonstrate that sildenafil citrate is intrinsically stable and not sensitive to light. On the basis of the stability studies described above, it is concluded that sildenafil citrate is stable under recommended storage conditions of temperature and relative humidity and justify the proposed retest period.

Drug Product

- Pharmaceutical Development

Several strengths of conventional immediate release white film-coated round biconvex tablets containing sildenafil citrate were studied in development for potential commercial presentation. All these strengths were prepared from a common blend of the active substances, which is qualitatively, and quantitatively equivalent to the blend used to produce Viagra tablets.

The only differences between Viagra tablets and Revatio tablets are the replacement of the blue dye in the film-coat with additional titanium oxide to give a white film-coat, and a change in the tablet shape and debossing.

Changes in the tablet formulation from clinical development to the commercial presentation are minor. The batches used in clinical trials only differ slightly in coating thickness and tablet dimension from the proposed commercial formulation. These changes are not considered to affect the bio-availability. Comparative dissolution results that have been provided confirm this.

The tablet cores contain cellulose microcrystalline and calcium hydrogen phosphate (anhydrous) as diluents, crosscarmellose sodium as disintegrant and magnesium stearate as lubricant. A two stage tablet coating employs an aqueous suspension of Opadry White followed by a clear coat of Opadry Clear. Both Opadry formulations contain glycerol triacetate and hypromellose whilst Opadry White also contains titanium dioxide and lactose.

All excipients chosen are well-known and comply with the Ph Eur, except from the printing ink. The choice and function of the excipients in the formulation has been described.

Except from lactose monohydrate used in the film-coating no excipients are of animal or human origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products'.

The plastic material used in the primary packaging, i.e. PVC, complies with the relevant Ph Eur monograph.

- Manufacture of the Product

The proposed commercial manufacturing process involves standard technology using standard equipment: blending, roller compaction, sieving, tabletting, coating, and imprinting.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process. The manufacturing process has adequately been validated and is satisfactory.
The in process controls are adequate for this pharmaceutical form.
The batch analysis data show that can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for description, identification of sildenafil (IR), identification of citrate (HPTLC), assay (95-105 % of the label claim, HPLC), uniformity of mass, water content, dissolution, total degradations products (HPLC), identity of titanium, and microbial purity.
The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.
Batch analysis data on eight batches (4 full scale and 4 pilot scale) confirm satisfactory uniformity of the product at release.

- Stability of the Product

The registration stability programme was designed to cover 20 mg, 40 mg and 80 mg tablets packed into HDPE bottles and PVC blisters. As all three strengths are manufactured from a common blend, all of the data from the registration stability programme is included to evaluate the stability of the product. The other strengths and containers studied are regarded as supportive data.

For the formal stability programme, three batches of 20 mg and 80 mg sildenafil citrate tablets were manufactured on production equipment at the proposed commercial manufacturing site at the intended commercial blend batch size. Three different lots of active substance were used.

The stability studies were carried out according to relevant CHMP/ICH stability guidelines at normal intermediate and accelerate ICH conditions for 6 months.

The following parameters have been tested: appearance, assay, degradation products, water content, hardness, dissolution, microbial quality and total degradation products.

One production batch of 20 mg and 80 mg has been stored for photostability at ICH conditions. The analytical methods are identical to those for release.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out 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.

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

3. Part III: Toxico-pharmacological aspects

Introduction

Viagra, which has already been authorised for the treatment of erectile dysfunction through the centralised procedure, also contains sildenafil. Only few non-clinical studies for Revatio have been conducted in addition to studies already performed for Viagra; 6 new pharmacology studies and 3 new pharmacokinetic studies. No new toxicology studies were conducted.

According to the applicant, toxicity and safety pharmacology studies were conducted in compliance with GLP regulations.

Pharmacology

- Primary pharmacodynamics *(in vitro/in vivo)*

Sildenafil inhibits phosphodiesterase (PDE) 5, thereby inhibiting the breakdown of cyclic guanine monophosphate (cGMP). Elevated cGMP reduces levels of intracellular calcium and thereby causes relaxation of these smooth muscle cells.

The N-desmethyl metabolite UK-103,320, has ca. 50% of the potency of sildenafil as a PDE5 inhibitor. An inhibition study on human recombinant cyclic nucleotide phosphodiesterase (PDE) enzymes 7 to 11 by sildenafil, or UK-103,320 clearly showed low inhibition properties of sildenafil and its major metabolite for PDE enzymes 7 to 11. However sildenafil does not act as a selective pulmonary vasodilator due to the widespread distribution of PDE5 in vascular smooth muscle containing tissues.

The effect of increasing doses sildenafil was tested on hypoxic pulmonary vasoconstriction (HPV) in the anaesthetised dog. In this model of pulmonary hypertension, caused by intermitted severe hypoxia, sildenafil attenuated HPV and reduced the pulmonary vascular resistance (PVR) even at the lowest dose tested (free plasma level below 5 nM). The response did not increase by increasing doses. It should be noted that intermittent hypoxia in man seems to exert only a small, probably clinical unimportant effect on pulmonary haemodynamics. Although in this model sildenafil has only a minor effect on systemic blood pressure vasodilator properties of sildenafil have been demonstrated in the anaesthetised dog at doses consistent with PDE5 inhibition. This implies a risk for adverse effects as facial flushing and headache.

- Secondary pharmacodynamics

Platelet aggregation experiments showed that sildenafil, in the presence of an NO donor, has an effect on platelets, with a possible antithrombotic effect but also a haemorrhagic risk. In animals, but not in humans, at least a trend in to increase bleeding times was found.

From studies in isolated gastrointestinal smooth muscle, it is clear that sildenafil can reduce gastrointestinal smooth muscle contractility most likely via the potentiation of the effects of NO, with a possible risk for inhibition of gastric emptying.

Sildenafil inhibits PDE6 in retina tissue at clinical relevant doses. Sildenafil had an effect *in vitro* on the response of the dog isolated retina to a blue light challenge and changed the ERG in anaesthetised dogs. Thus there is pharmacological basis for an effect on visual function.

A moderate affinity of sildenafil for some adenosine receptors was reported but it is 100-fold less than its activity against the human PDE5 enzyme.

- Safety pharmacology

The absence of PDE5 in cardiac muscle and the lack of effect on cardiac contractility suggest that sildenafil will not have adverse cardiac effects in pulmonary hypertension patients.

In line with sildenafil's haemodynamic profile, a modest antidiuretic effect was observed.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted. Clinical studies of sildenafil when co-administered with other medicinal products for the treatment of PAH have been planned.

Pharmacokinetics

The pharmacokinetic profile of sildenafil was studied in the mouse, rat, rabbit and dog.

- Absorption- Bioavailability

Sildenafil was rapidly and extensively absorbed from the gastrointestinal tract in all species studied. Due to substantial presystemic elimination, however, absolute bioavailability was 15-54%. A species-specific gender difference in bioavailability was apparent in the rat.

- Distribution

In vitro the mean proportion of sildenafil bound to plasma proteins was 94% (mouse), 95% (rat), 91% (rabbit), 86% (dog) and 96% (man). The *in vitro* whole blood : plasma ratio for sildenafil was 0.92 and 0.64 in beagle and human blood, respectively. Except for the rat, the free fractions for sildenafil and its pharmacodynamically active N-desmethyl metabolite UK-103,320 were similar. Sildenafil and UK-103,320 bound to human albumin and α1-acid glycoprotein. Sildenafil bound predominantly to albumin and UK-103,320 bound approximately equally to albumin and α1-acid glycoprotein.

Tissue distribution of ^{14}C-sildenafil was studied in pigmented and albino rats upon single i.v. or subcutaneous dosing. Radioactivity was widely distributed. In general, tissue concentrations of radioactivity in female rats were higher than those in males, and declined more slowly. Concentrations of radioactivity in rat brain were about 50% or less of those seen in blood. Concentrations in CSF were only 1-3% of those in plasma. By 24 h post-dose, residual radioactivity was limited mainly to the retina, substantia nigra and pigmented skin, suggesting that sildenafil and/or its metabolites bind to melanin. The concentration of radioactivity in albino rats declined more rapidly compared with pigmented animals.

- Metabolism *(in vitro/in vivo)*

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. Male and female rats did not differ with respect to patterns of metabolites.

In vitro studies with human microsomes showed that the metabolism of sildenafil to UK-103,320 is mediated by CYP2C9 (high affinity, low capacity) and CYP3A4 (low affinity, high capacity). CYP3A4 appears the more important isoenzyme at clinically relevant concentrations. For human metabolism the most relevant pathways are the piperazine N-demethylation into UK-103,320 and piperazine N,N-deethylation into UK-150,564. The proposed mechanism of the formation of both UK-103,320 and UK-150,564 via a common event by formation of a common unstable intermediate seems plausible. Further, CYP3A4 and CYP2C9 being the most relevant enzymes corresponds to the results from interaction studies.

- Excretion

In all species investigated, the predominant route of excretion was the faeces, which accounted for 71-85% of the dose. The majority of excreted radioactivity was recovered within the first 48 hours. No studies were conducted on enterohepatic cycling.

In male rats, a higher plasma clearance, shorter elimination half-life and lower bioavailability of sildenafil was observed as compared with females reflecting a species-specific gender difference in metabolic clearance.

- Pharmacokinetic drug interactions

The most potent inhibitors of sildenafil metabolism in human liver microsomes were ritonavir, itraconazole and ketoconazole (IC_{50} < 0.05 μM). Also potent inhibitors were indinavir and nelfinavir (IC_{50} of both substances < 1 μM) and saquinavir (IC_{50} 5 μM). Cimetidine showed only limited potency to inhibit sildenafil metabolism (IC_{50} 700 μM).

Toxicology

Toxicokinetics were sufficiently monitored to base dose extrapolation on. In all toxicity studies, the levels of systemic exposure were adequate.

- Single dose toxicity

Single dose toxicity was low as tested in both rats and mice employing the p.o. and i.v. routes of administration. Lethality after oral administration occurred at 1000 mg/kg and 500 mg/kg in rats and 1000 mg/kg in mice. Clinical signs, which preceded mortality, were partially closed eyes, hunched posture, tremors and depression.

- Repeat dose toxicity

Repeated p.o. dose toxicity was extensively studied in mice (for three months), rats (for up to 6 months), and beagle (up to 12 months). In addition, some relatively short-term studies (up to 1 month) were conducted in rats and beagles employing the i.v. route of administration.
Mice were particularly sensitive as they died probably because of marked gastrointestinal dilation already at low dose levels leaving no AUC-based safety margin (see also "Carcinogenicity" section). This effect was due to the exaggerated pharmacodynamic action of UK-92,480 resulting in a prominent reduction in transit time. This severe toxicity was not confirmed in other animal species nor in man.
In rats, the main findings were anaemia, centrilobular hypertrophy in the liver, follicular cell hyperplasia in the thyroid, and hypertrophy of the zona glomerulosa in the adrenal cortex. The margin of safety was adequate. In addition, the kidney was occasionally identified as a target as well, although microscopic evidence of kidney changes (i.e. an increased incidence of glomerulonephrosis) only occurred in the 6-month rat study. Clinical chemistry revealed a decrease in triglycerides and an increase in cholesterol levels in rats. The thyroid hypertrophy was shown to be a secondary response to liver enzyme induction (see also "Carcinogenicity" section). The adrenal hypertrophy of the zona glomerulosa may be the result

of the vasodilatory properties of sildenafil through activation of the renin-angiotensin-aldosterone system, a reflex response to a prolonged reduction in blood pressure.
Occasionally, a low incidence of mesenteric arteritis was seen in rats at high dose levels only. It was only found in the 1-month study, and did not occur in the subsequent rat studies where mesenteric arteries were specifically examined. Again at high dose levels, arteritis was also encountered in beagles, more frequently than in rats. The arteritis was mainly seen in the coronary arteries, but occasionally disseminated necrotising panarteritis was observed upon long-term administration as well. In both rats and beagles, arteriopathy has been reported in the open literature not only for PDE inhibitors, but for other vasodilators as well. The arteriopathy probably is due to a reflex response to the exaggerated haemodynamic action of sildenafil, although the beagle studies failed to show a consistent effect on blood pressure. In the literature, it has been suggested that prolonged reductions in blood pressure, together with alterations in intramural tension resulting from vasodilatation, may be involved in the pathogenesis of vasodilator-induced arteriopathy. Alternatively, the arteriopathy in beagles may be designated as idiopathic juvenile arteritis ("beagle pain syndrome"). This dog-specific syndrome is thought to be an expression of a latent disease aggravated by stress, rather than a direct toxic effect of the test compound. Whatever the mechanism may be, the arteriopathy seen in rats and beagles is not considered relevant to man, due to the high safety margin, and the low incidence with no clear relationship to dose.
In dogs, heart rate was moderately increased in all studies, with no consistent changes in blood pressure.
Although in the clinic abnormal vision has been reported, ophthalmological and histopathological examinations have not revealed unusual ocular findings in the animal toxicity studies. It should be noted that the number of photoreceptors was not examined because this was technically impossible. Instead, the inner and outer nuclear layers of the retina were counted as an indirect indicator of the integrity of the photoreceptor layer.
No adverse effect levels in the rat and dog were 60 mg/kg and 15 mg/kg respectively, which corresponds to more than 10 times the human AUC of free sildenafil.

- Genotoxicity *in vitro* and *in vivo*

Sildenafil did not induce mutations in bacterial or mammalian cells in vitro, nor did it cause clastogenic activity in vivo or in vitro.

- Carcinogenicity

The carcinogenic potential was studied in mice and rats. The mouse study was negative for carcinogenic findings. The most important adverse effect of sildenafil in mice (particularly the males) was an increase in mortality due to marked gastrointestinal dilation (see also "Repeat Dose Toxicity" section). A second mouse study, with lower dosages and no difference in mortality between the groups, was also negative. In high-dose male rats, there was a statistically significant positive trend for thyroid follicular cell proliferative changes. This was mainly related to an increase in follicular cell hyperplasia. The underlying mechanism is probably an increased turnover of thyroid hormones due to hepatic enzyme induction, which bears no relevance to man. Evidence for this mechanism was provided (see also "Repeat Dose Toxicity" section).

- Reproductive and developmental studies

In the segment I and II studies no remarkable toxicity was found in the offspring even in the presence of maternal toxicity. In the pre- and postnatal toxicity study in rats, a decrease was observed in mean litter size, in body weight gain in the first 14 days and, in 4-day survival. Dilatation of the ureter, and delay in the appearance of upper incisors and in the attainment of the air righting reflex were also observed. Foetal ureter and dilatation was also visible in the rat segment II study. In male pups, a delayed attainment of the air righting reflex occurred already at the lowest dose of 10 mg/kg. For female pups, the assessed exposure safety margin was between 7 and 19 with the decreased 4-day survival as critical effect. No sperm analysis was conducted.

The ureter effects seem to be a treatment-related effect. At the dosage used, the exposure multiple compared to humans is sufficiently high that it probably bears little relevance to humans.
A diminished blood supply to the uterus and placenta caused by sildenafil can be considered unlikely.
The mechanism involved in the high dose effects observed in the pre- and postnatal study may be related to inhibition of oxytocin-induced contractions in the rat uterus, demonstrated in vitro.

- Local tolerance

Sildenafil produced no vascular irritation after intra-arterial injection in rabbits.

- Other toxicity studies

No studies were conducted in juvenile animals.

No studies were performed on immunotoxicity. This is acceptable because no signs of immunotoxicity were observed in the preclinical studies.

Studies on impurities

The impurity UK-263,909 is specified at 0.3%. This impurity was toxicologically qualified up to 0.3%. All other impurities are limited to 0.1%, which is lower than the qualification limit.

Ecotoxicity/environmental risk assessment

An environmental risk assessment was provided and accepted.

Discussion on the non-clinical aspects

The overall profile of sildenafil suggests that it is a potent, orally-active agent which relaxes pulmonary vascular smooth muscle, prevents platelet-based obstructions to blood flow in the presence of NO and relaxes peripheral blood vessels. Several possible adverse reactions (vasodilatation, antidiuretic effect, haemorrhagic risk, inhibition of gastric emptying and visual disorder) can be associated with the use of sildenafil in view of its pharmacological profile.

Repeated dose toxicity, genotoxicity and carcinogenicity studies did not reveal special hazards for humans.

In pups of rats which were pre- and postnatally treated with 60 mg/kg sildenafil, a decreased litter size, a lower pup weight on day 1 and a decreased 4-day survival were seen at exposures which were approximately fifty times the expected human exposure at 20 mg TID. These effects were observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Due to lack of data, Revatio should not be used in pregnant women unless strictly necessary.

4. Part IV: Clinical aspects

Introduction

More than thirty clinical pharmacology studies were conducted in the original sildenafil male erectile dysfunction (MED) development program. Of these, 24 are considered to support the proposed label for treatment of PAH. Fifteen clinical pharmacology studies were conducted post-approval of sildenafil in MED. One new clinical pharmacology study (bosentan-sildenafil interaction) was conducted specifically for the PAH development program.

The PAH development program essentially consists of 2 studies in adults with PAH. Study A1481140, was the pivotal 12-week placebo-controlled dose ranging study, after which patients could enter a

long-term extension study A1481142. Study A1481141, exploring the use of sildenafil in combination with intravenous epoprostenol was still ongoing at the time of the marketing authorisation evaluation.

The safety and efficacy of sildenafil in children with pulmonary hypertension is not yet known, but it is being evaluated in 2 ongoing paediatric trials. An indication for paediatric patients was not requested in the current application.

According to the applicant, all clinical studies conformed to ICH Good Clinical Practice (GCP) standards and were conducted according to the Declaration of Helsinki (Edinburgh 2000 revision).

Pharmacokinetics

Pharmacokinetic data on sildenafil are mainly based on studies in healthy volunteers in the framework of the MED dossier, except for the interaction study with bosentan and the population pharmacokinetics analysis of clinical studies 1140 and the main pharmacodynamic study (1024).

- Absorption

Absolute bioavailability of sildenafil is approximately 40%, where first pass metabolism is almost completely responsible for the reduced bioavailability. Maximal plasma concentrations are reached one hour after oral administration of the tablet. Simultaneous intake of food delays absorption (approximately with 1 h and C_{max} is 29% lower) and lowers the extent of absorption marginally (ca. 11%). Food intake is not expected to affect steady state concentrations in a clinically relevant way. Population PK data support this finding.

Based on population pharmacokinetic analysis, average plasma concentrations were 20% to 50% higher in PAH patients. Mean maximum exposure at steady state of sildenafil is 113 ng/ml after three times daily dosing of 20 mg. The 80 mg TID dosing led to a 40% higher exposure, i.e. not dose proportional, relative to 20 mg and 40 mg TID. There was a five-fold difference in exposure for the 80 mg TID dosing as compared to the recommended 20 mg TID dosing schedule.

- Distribution

Sildenafil has a volume of distribution of approximately 105 L, and a 95% protein binding. However, sildenafil only occupies a limited proportion of protein binding sites and is not expected to have an impact on protein binding of other drugs. Renal or hepatic impairment does not seem to affect protein binding of sildenafil and its main metabolite UK-103,320. Free fractions of sildenafil and UK-103,320 in young volunteers were approximately 1 % higher then in elderly volunteers (>65 years).

- Elimination

Sildenafil is metabolised extensively in the liver, predominantly mediated by two cytochrome P450 isoforms; CYP2C9 and CYP3A4. The main metabolite UK-103,320 has a plasma concentration of less than 50% of sildenafil in healthy volunteers and its pharmacological activity as a PDE inhibitor is half that of the parent compound. There is an increased concentration (up to 73% of the parent compound) of the metabolite in patients with PAH. UK-103,320 therefore probably contributes to the pharmacological efficacy.

After oral administration sildenafil is excreted predominantly in the faeces (80%) and to a smaller extent in urine (13%).

- Dose proportionality and time dependencies

In the range of 25 - 100mg orally once daily administered, sildenafil rate and extent of absorption are dose-proportional. Above this range, absorption increases to a somewhat greater extent (1.16 times the dose for AUC) than the dose is increased.

Steady state concentrations are reached on the second day after three times daily dosing, which fits to a $t_{½}$ of 4h. Accumulation after multiple dosing is 36%-50%.

- Special populations

Severe renal impairment led to an approximately 100% increase in sildenafil exposure. Sildenafil exposure was increased by 85% in elderly subjects (65 and up) and in subjects with mild to moderate hepatic impairment (Child-Pugh A or B).

Simulations based on these population PK data with alternative dosing schedules with 20 mg BID or 20mg OD compared with thrice daily doses led to considerably lower average and minimum plasma sildenafil exposure in these patient groups. With a BID dosing schedule sildenafil plasma levels reached roughly two-thirds of that of the TID dosing schedule. The effect of the simulations on C_{max} was negligible in the selected patient groups with a larger effect on C_{min}.

The clinical relevance of these almost two-fold increases in sildenafil exposure were discussed. In the pivotal study 1140 and its extension study 1142 doses up to 80 mg TID were used and 80 mg TID dose leads to a 5-fold higher exposure than the recommended 20 mg dose, which was well tolerated. There is therefore a wide safety margin for sildenafil 20 mg TID. Neither age, renal or hepatic impairment, as covariates, significantly affected sildenafil pharmacokinetics in patients with PAH, in a validated population kinetic model. All age groups (up to 75 years) and patients with renal impairment with a creatinine clearance > 30 ml/min were well-represented. Therefore, dose adjustments are not considered necessary in the elderly and patients with mild-to-moderate (>30 ml/min) renal impairment.

Only two patients in study A1481140 had a creatinine clearance below 30 ml/min. Impact of hepatic impairment was studied by individual laboratory parameters (AST, ALT, bilirubin and ALKP) and no signal was shown but it is not sufficient to exclude potential effect. For these particular subgroups of patients, observed high plasma exposure (85-100% increased AUC, 47-88% increased C_{max}) should be carefully considered.

Since underdosing in patients with the serious disease should be avoided and there is no clinical efficacy data in PAH patients on dosing regimens below 20 mg TID, sildenafil 20 mg TID would be an acceptable starting dose for patients with severe renal impairment and patients with mild-to-moderate hepatic impairment (Child Pugh classes A and B). Nevertheless, downtitration should be considered in case of intolerance.

Due to the lack of data, sildenafil should be contraindicated in patients with severe hepatic impairment (Child Pugh class C).

No impact on pharmacokinetics was observed in female compared to male patients.

No pharmacokinetic studies were performed in children.

- Pharmacokinetic interaction studies

In-vitro sildenafil has been shown to be metabolized primarily by the CYP3A4 isoenzyme and to a lesser extent by CYP2C9. The in-vivo studies and the population pharmacokinetic analysis of the pivotal study confirmed that CYP3A4 was the most relevant metabolic pathway.

Sildenafil (80 mg TID at steady state) increases bosentan exposure by approximately 50% while sildenafil exposure itself decreases by approximately 60% when co-administered with bosentan. Bosentan is an inducer of CYP2C9 and CYP3A4. The pharmacokinetic interaction of bosentan and sildenafil is of importance since their co-administration cannot be excluded despite the current lack of clinical efficacy and safety data. Due to the complicated pharmacokinetics of sildenafil (possible saturation of metabolising enzymes) and bosentan (CYP auto-induction), and, the absence of efficacy and safety data on co-administration in patients with PAH, it is difficult to anticipate the actual clinical

response. In the SPC it should be stated that currently no data are available from patients with PAH regarding the efficacy and safety of sildenafil in co-administration with other treatments such as bosentan, iloprost and epoprostenol.
Co-administration of ritonavir (500mg BID) a potent CYP3A4 and CYP2C9 inhibitor increased sildenafil (100 mg single dose) AUC 11-fold and Cmax 4-fold. Saquinavir (1200mg TID), a CYP3A4 inhibitor, led to a 140% increased Cmax and 210% increased AUC of sildenafil. A similar increase, AUC with 180%, was observed when erythromycin (CYP3A4 inhibitor) was co-administered. Potent CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have effects similar to ritonavir. Co-administration ritonavir and that of other potent CYP3A4 inhibitors (ketoconazole, itraconazole) should be contra-indicated. In contrast with sildenafil's isolated use in MED, accumulation may occur after repeated dosing intended for treatment of PAH. Prolonged exposure to very high plasma sildenafil levels bears unacceptable safety concerns. CYP3A4 inhibitors of intermediate potency (e.g. clarithromycin, telithromycin and nefazodone) are expected to have an effect in between that of ritonavir and CYP3A4 inhibitors of medium potency (e.g. saquinavir/erythromycin), a seven-fold increase in exposure is assumed. Therefore dose adjustments should be recommended when using CYP3A4 inhibitors of intermediate potency.
Cimetidine (800 mg) a non specific cytochrome P450 inhibitor led to a 56% increased sildenafil AUC. The impact of grapefruit juice (a weak CYP3A4 inhibitor) was not investigated. Population PK data showed that the frequently observed co-administration of CYP3A4 substrates led to a 43% increased sildenafil plasma concentration.
In turn sildenafil did not affect steady-state concentrations of CYP3A4 substrates ritonavir and saquinavir.
In the population PK analysis, CYP3A4 substrates alone or in combination with beta-blockers increased sildenafil exposure by 43% and 66% respectively.
The proportion of patients receiving CYP3A4 inducers in the PK population analysis was small, but had a substantial impact on sildenafil pharmacokinetics. This impact concurs with the findings of the bosentan interaction study. Therefore, treatment should be closely monitored in patients using concomitant potent CYP3A4 inducers, carbamazepine, primidone, phenytoin, pyrazinamide and rifampicin.
Sildenafil (50 mg) had no clinically relevant impact on CYP2C9 substrates tolbutamide (250 mg), and warfarin (40mg).
Co-administration of azithromycin, antacids (Maalox), amlodipine, doxazosin, atorvastatin, and oral contraceptives (Microgynon) did not affect sildenafil pharmacokinetics or vice versa.

Pharmacodynamics

- Mechanism of action

In the human lung, endothelium-derived nitric oxide (NO) activates soluble guanylate cyclase, increasing cyclic guanosine monophosphate (cGMP) production, which opens potassium channels via cGMP kinase causing pulmonary vasorelaxation. Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) enzyme phosphodiesterase 5 (PDE5), resulting in vasodilatation through the NO/cGMP pathway at sites expressing this enzyme. Since the pulmonary epithelium contains substantial levels of PDE5, the potential clinical benefit of sildenafil in the treatment of PAH was investigated.

- Primary and Secondary pharmacology

The main pharmacodynamic study was A1481024 that investigated key haemodynamic parameters such as pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) in patients with PAH during administration of various doses of intravenous sildenafil yielding a wide range of plasma concentrations between 10-500ng/ml. This study comprised only a limited amount of patients per treatment group ($n \leq 14$). Maximum reductions in the relevant pulmonary parameters mean PVR and mean PAP appeared to be reached at plasma sildenafil concentrations of 100 ng/ml, while reductions in mean systemic blood pressure were only minor at concentrations $\leq$ 100 ng/ml (in patients without NO). No clinically significant mean changes were observed in patients receiving placebo. This study therefore indicated that oral dosages yielding plasma levels up to 100 ng/ml could comprise a

clinically useful dose range containing relative selectivity to the pulmonary circulation. Mean heart rate remained stable across the entire dose range of 10-500ng/ml in all subjects, and mean absolute values of cardiac output tended to increase across a dose range of 10-100ng/ml, but appeared to plateau at higher dosages. No clinically significant changes in blood gasses (PaO2, mVO2, Sp02) were observed, indicating no beneficial effects of sildenafil on the oxygenation status of patients with PAH.

Calculations from multiple dose PK study 148-207 indicated that sildenafil 40 mg TID would yield an expected peak total plasma concentration of 248 ng/ml, an average total plasma concentration of 93 ng/mL, and a trough concentration of 28.2 ng/ml. With 20 mg TID, the expected peak total plasma concentration is 113 ng/ml, the average total plasma concentration 40.3 ng/ml, and the trough concentration 14.1 ng/ml. Thus, in view of these PK data and the data derived from PD study A1481024, a dose range around 20-40 mg TID would be appropriate for clinical testing, as this could yield (average) plasma concentrations within a potentially clinically appropriate plasma concentration range of 10-100 ng/ml. It should however be noted that despite this frequent dosing schedule (three times daily), the peak to trough plasma concentration ratio is still considerable due to the short terminal half life of sildenafil (3-5 hours), rendering sildenafil generally less suitable for 24-hr prophylactic treatment.

As previously described in the labelling for Viagra, PD studies comprising visual function tests showed mild and transient differences in colour discrimination in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. These events were described mainly as difficulty in discriminating colours, colour-tinged vision, halo and increased perception of brightness. Meanwhile, healthy volunteer PD study 148-207 did not indicate an impact on colour discrimination after 8 days of chronic sildenafil dosing up to 75mg TID. The postulated mechanism for this change in colour discrimination at dosages of at least 100mg is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Further ophthalmic testing was also performed in the main clinical studies in patients with PAH chronically treated with sildenafil 20-80mg TID (see section on Clinical Safety).

Pharmacodynamic interactions

Pharmacodynamic interactions have focused on the impact of sildenafil on bleeding (warfarin, acenocoumarol, phenprocoumon, aspirin) and haemodynamics (GTN, ISMN, doxazosin, amlodipine, alcohol). In none of the studies focusing on bleeding wasa clinically significant potentiation on bleeding time / INR observed, either when co-administered with vitamin K-antagonists or aspirin.

Sildenafil, through its effect on the NO/cGMP pathway, potentiates the hypotensive effects of nitrates and this concomitant use is therefore rightfully contra-indicated. Co-administration of alcohol and amlodipine did not potentiate the BP lowering effect of sildenafil alone. Co-administration of sildenafil with the alpha-blocker doxazosin did not potentiate the hypotensive effect of either drug but symptomatic hypotensive effects cannot be excluded in susceptible subjects. As a consequence, sildenafil should be contra-indicated in patients with severe hypotension (BP <90/50 mmHg) and caution should be advised when sildenafil is administered to patients taking an alpha-blocker.

Clinical efficacy

- Main study

Pivotal study A1481140:

This was a multinational, multi-centre, double-blind, double-dummy, parallel group study investigating the effect of three dose levels of sildenafil and placebo on exercise capacity in patients with PAH (n=277). After 12 weeks in this study, patients could enter the extension study A1481142.
Methods

Study Participants

Inclusion criteria included:

- Subjects aged 18 and over who had any of the following conditions: Primary pulmonary hypertension (PPH), PAH with connective tissue disease (CTD) or PAH with surgical repair, at least 5 years previously, of heart lesions (atrial septal defect; ventricular septal defect; patent ductus arteriosus; or aorto-pulmonary window).
- Subjects with a mean PAP (pulmonary artery pressure) ≥25mmHg and a pulmonary artery wedge pressure (PAWP) of ≤15mmHg at rest, assessed via right heart catheterisation within 21 days prior to randomisation.
- Subjects whose baseline 6-Minute Walk test distance was ≥100m and ≤450m.

Exclusion criteria included:

- PAH secondary to any aetiology other than those specified in the inclusion criteria.
- Significant (*ie* >2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation,
- Acute decompensated heart failure within the previous 30 days.
- Left ventricular ejection fraction less than 45% or left ventricular shortening fraction less than 0.2 within the three months prior to study enrolment.
- Creatinine clearance less than 30ml/min.
- Hypotension (systolic arterial pressure less than 90mmHg).
- Severe impairment of hepatic function.
- Pregnant or lactating women.

Treatments

Subjects were randomised to one of four treatment groups: placebo, sildenafil 20mg, sildenafil 40mg, or sildenafil 80mg). Subjects who were randomised to sildenafil 80mg received 40mg for the first seven days and then underwent an up-titration to 80mg. Subjects randomised to placebo, sildenafil 20mg or sildenafil 40mg underwent a dummy up-titration after seven days.

Sildenafil was added to existing PAH therapy but the administration of bosentan and prostacyclin was forbidden.

Objectives

The primary objective was to evaluate the effect of three doses of oral sildenafil on exercise capacity, as measured by the 6-Minute Walk test, after 12 weeks of treatment in subjects with PAH who were aged 18 years and over.

Secondary objectives included assessment of the safety and tolerability, investigation of plasma concentration-effect relationship and determination of the population pharmacokinetic parameters.

Outcomes/endpoints

The primary endpoint was the change from baseline in the total distance walked in 6 minutes at Week 12.

Secondary endpoints included: mean pulmonary arterial pressure (PAP), time to clinical worsening and BORG dyspnoea score. Other descriptive variables were WHO pulmonary hypertension criteria for functional capacity and therapeutic class, haemodynamic measurements (such as cardiac output [CO], right atrial pressure [RAP], pulmonary capillary wedge pressure [PCWP], pulmonary vascular resistance [PVR]); and Quality of Life (measured by the Short Form Health Survey (SF-36), the EuroQOL 5-Dimensions and patient overall preference assessment at the end of treatment).

Sample size

Assuming a treatment effect for sildenafil of 55 metres over placebo and a standard deviation of 75 metres, a sample size of 60 subjects per treatment group was required to detect this difference with 90% power at a one-sided significance level of 0.005 (which corresponds to a two-sided significance level of 0.01).

Randomisation

Subjects were randomised to one of the 4 treatment groups in a 1:1:1:1 ratio. The following 2 stratification factors were used: Aetiology of PAH (PPH, PAH secondary to connective tissue disease, PAH with surgical repair) and Baseline exercise capacity (<325m, ≥325m). The main reason to include a covariate in the analysis was the existence of a strong or moderate association between the covariate and the primary outcome measure.

Statistical methods

The primary endpoint was evaluated using a one-sided sequential step-down testing procedure in which the mean response in each sildenafil dose group was compared to that in the placebo group in a step-down fashion. First the highest dose group (80 mg TID) of sildenafil was compared to placebo. If no significant benefit was achieved, no further tests were to be carried out. If a significant benefit was achieved, then the next dose group (40 mg TID) was compared to placebo. Similarly, the 20 mg dose group was only compared to placebo if a significant benefit was achieved for the 40 mg group. All the pairwise comparisons described above were carried out at the pre-specified one-sided alpha level of 0.005 (which corresponds to a two-sided alpha of 0.01). The primary analysis was carried out using a two-sample *t*-statistic, stratified for baseline walking distance and aetiology for the ITT and PP populations. In the ITT (Intent-to-treat) analysis, subject with a missing Week 12, 6-Minute Walk Test had an assessment imputed using the LOCF. Normality of the primary endpoint was investigated graphically for both the ITT and PP (per protocol) populations.

Secondary endpoints were subjected to statistical testing in a hierarchical order as follows: mean pulmonary arterial pressure (PAP), time to clinical worsening and BORG dyspnoea score.
Mean PAP was evaluated using a stratified t-test, time to clinical worsening was evaluated using a stratified log-rank test and BORG dyspnoea score was evaluated using a stratified Wilcoxon test. The stratification factors for each analysis were baseline walking distance and aetiology (as specified for the primary endpoint). All pairwise comparisons within each secondary endpoint were performed at the one-sided alpha level of 0.025.

RESULTS

A total of 360 subjects were screened, there were 82 screen failures Two hundred and seventy eight subjects (278) were randomised to receive placebo (70 patients), sildenafil 20mg (69 patients), 40mg (68 patients) or 80mg (71 patients) TID; one subject randomised to receive sildenafil 40mg did not receive treatment. 277 randomised subjects took at least one dose of study medication.

The number of patients who discontinued the study prematurely was similar in each treatment arm: placebo (2.86%), 20 mg sildenafil TID (2.9%), 40 mg sildenafil TID (3%), 80 mg sildenafil TID (8.5%). Of the 12 patients who discontinued prematurely, the greatest number withdrew due to AE not related to treatment (1.44%).

Baseline data

All 4 treatment groups had a comparable composition regarding primary diagnosis and demographic characteristics. Overall, a majority of patients was female (n=209, 75%) and had primary PAH (n=175, 63%) or CTD-associated PAH (n=84, 30%). Patients with surgical repair-associated PAH merely represented 6% of the population. Most patients had WHO functional class III (58%) or II (39%), while patients in WHO class I and IV (0.4% and 3%, respectively) were very poorly represented in the ITT sample. The mean baseline walking distance approximated 345 meters.

Outcomes and estimation

Primary Endpoint

The primary efficacy endpoint of the study was the change from baseline in exercise capacity at Week 12 as measured by distance walked in six minutes.
Mean placebo-corrected treatment effects of 45.3 metres (99% CI: 20.5, 70), 46.1 metres (99% CI: 19.9, 72.4) and 49.7 metres (99% CI: 22.9, 76.5), were seen in favour of sildenafil 20 mg (P <0.0001), sildenafil 40 mg (P <0.0001), and sildenafil 80 mg (P<0.0001), respectively. A 'sensitivity analysis' was carried out on all randomised and treated subjects in which subjects who did not have any post-baseline 6-Minute Walk test assessments and subjects who died during the study had their 6-Minute Walk test distance at Week 12 set to the baseline result, whilst all other subjects used their Week 12 6-Minute Walk test or had their last observation carried forward. Results are presented in the figure and tables below:

Treatment comparisons of the primary endpoint

	Treatment Comparison With Placebo		
	Sildenafil 20mg	**Sildenafil 40mg**	**Sildenafil 80mg**
ITT Population (Placebo N=66)	N=67	N=64	N=69
Mean Difference (SE)	45.3 (9.6)	46.1 (10.2)	49.7 (10.4)
p-value from stratified t-test (1-sided)	<0.0001	<0.0001	<0.0001
99% Confidence Interval	(20.5, 70.0)	(19.9, 72.4)	(22.9,76.5)
ITT Population - Sensitivity analysis (Placebo N=66)	N=68	N=65	N=71
Mean Difference (SE)	43.2 (9.6)	45.4 (10.1)	48.8 (10.3)
p-value from stratified t-test (1-sided)	<0.0001	<0.0001	<0.0001
99% Confidence Interval	(18.6, 67.9)	(19.4, 71.5)	(22.3 , 75.2)

The primary ITT analysis showed a statistically significant and clinically relevant mean placebo-corrected sildenafil treatment effect on the 6-Minute Walk Test distance of 45-50 meters in all active treatment groups. The results from a 'sensitivity analysis' (n=270) and the per protocol population analysis (n=161) both confirmed the results on the aforementioned ITT analysis.

The largest part of the treatment effect was already seen at Week 4 after randomisation, after which a lesser increase was noted up to Week 12, indicating the absence of medium-term pharmacological tolerance.

Secondary endpoints

Subjects on all sildenafil doses achieved a statistically significant reduction in mean PAP compared to those on placebo. The baseline mean PAP was 53 mmHg, and the change from baseline in mean PAP was -2.1 mmHg at the proposed sildenafil dose of 20mg TID and there was some evidence for a dose-dependent decrease in mean PAP.

A statistically insignificant decreased incidence of 'clinical worsening events' in the active treatment groups as compared to placebo was obtained (see table below), primarily driven by reduced hospitalisations (7% with 80 mg, 3% with 40 mg, 4% with 20 mg and 10% with placebo).

Incidence of Clinical Worsening Events

Reason for Clinical Worsening	**Placebo (N=70)**	**Sildenafil 20mg (N=69)**	**Sildenafil 40mg (N=67)**	**Sildenafil 80mg (N=71)**
(a) Worsening* (N (%))	7 (10)	3 (4)	2 (3)	5 (7)
Death	1 (1)	1 (1)	0 (0)	2 (3)
Lung Transplantation	0 (0)	0 (0)	0 (0)	0 (0)
Hospitalisation due to PAH	7 (10)	2 (3)	2 (3)	2 (3)
Initiation of Prostacyclin Therapy	1 (1)	0 (0)	0 (0)	0 (0)
Initiation of Bosentan Therapy	0 (0)	0 (0)	1 (2)	2 (3)

* Subjects who had more than one clinical worsening event were counted separately under each type of event they experienced (but the total number only counted subjects once, irrespective of the number of events they had).

Since no statistically significant treatment benefit was observed in time to clinical worsening, statistical testing was not carried out on BORG dyspnoea score.

The percentage of subjects on each of the sildenafil doses that showed an improvement of at least one functional class over the 12-week period was greater compared to placebo (42% with 80 mg, 36% with 40 mg, 28% with 20 mg and 7% with placebo).

Ancillary analyses

Results were generally consistent in subgroups according to baseline walking distance, aetiology (primary and CTD-associated PAH), gender, race, location, mean PAP and PVRI. There was a suggestion of an effect modification with age, in a sense that elderly patients appeared to experience a lesser improvement in exercise capacity.

- Supportive study

A large majority of patients randomised in the pivotal trial A1481140 was subsequently included in extension study A1481142 (n=259), in which patients were titrated to sildenafil 80mg TID if tolerated. Alternative PAH therapy was permitted (e.g. epoprostenol, iloprost), except bosentan. A majority of patients (94%) reached a final dose of 80mg TID, indicating that the high dose was reasonably well tolerated. Subjects who received placebo in study A1481140 and reached a dose of 80mg TID at Week 24, showed a mean increase from baseline of 46 meters in 6-Minute Walk Test distance at Week 24, which is comparable to the improvement seen in the sildenafil 20-80 mg TID dose groups from baseline to Week 12 in study A1481140 (i.e., 41-47 m). In agreement with this, subjects randomised to sildenafil 20-80mg TID in study A1481140 who received a dose of 80mg TID at Week 24, had a mean increase from baseline to Week 24 in 6-Minute Walk Test distance of approximately 50 meters.

- Discussion on clinical efficacy

Pivotal study A1481140 was a double-blind, double-dummy, parallel group study with three sildenafil dose levels (20, 40 and 80 mg TID) and placebo in patients with PAH (n=277).

Based on inclusion and exclusion criteria, only patients with idiopathic PAH, PAH with CTD, and PAH with surgical repair entered in the study. Consistent with the accepted definition of pulmonary hypertension, a mean resting PAP >25 mmHg was required. In view of the potential clinically relevant dose range of 20-40mg TID derived from the PD studies A1481024 and 148-207, the dose of 80mg TID seems unnecessarily high from an efficacy point of view, but could yield valuable safety data.

The 6-Minute Walk Test (primary endpoint) is the most widely used test to assess exercise capacity in PAH trials. The primary ITT analysis showed a statistically significant and clinically relevant mean placebo-corrected sildenafil treatment effect on the 6-Minute Walk Test distance of 45-50 meters in all active treatment groups. The results from a 'sensitivity analysis' and the per protocol population analysis both confirmed the results on of the analysis. The largest part of the treatment effect was already seen at Week 4 after randomisation, after which a lesser increase was noted up to Week 12, indicating the absence of medium-term pharmacological tolerance. No substantially increased treatment effect beyond a sildenafil dose of 20mg TID was obtained regarding the primary endpoint. The selected dose range therefore yielded efficacy results on the higher end of the dose-response curve. As no data are available at a sildenafil dose range below 20mg TID, the lowest effective dose in PAH patients remains unknown.
There was a statistically significant reduction in mean PAP compared to those on placebo (-2.1 mmHg) at the proposed sildenafil dose of 20mg TID. There was some evidence for a dose-dependent decrease in mean PAP, but this was not reflected in a dose-dependent increase in exercise tolerance, as judged from the ITT analysis on the primary study endpoint. There was no clear evidence that sildenafil 20-80mg TID reduced the level of dyspnoea in patients with PAH.

The study duration of 12 weeks is considered sufficient to provide efficacy results of clinical relevance, but the demonstration of long-term efficacy would require considerably longer treatment duration.

Regarding patients in WHO class II, the pivotal trial likely included mainly severe class II cases, which may not be representative of functional class II population in clinical practice.

The wording of the indication was revised to reflect the studied population considering that different responses to sildenafil could be anticipated depending on disease severity (as reflected in WHO functional classification) and/or aetiology.

Data from the extension study further indicated that a sildenafil dose range of 20-80 mg TID is at the higher end of the dose-response curve and that a sildenafil dose level of 80mg TID is associated with a 6-month sustained improvement of ~50 meters. However, no placebo or active control arm was included in this open-label extension study, precluding firm conclusions on the maintenance of efficacy after 12 weeks of treatment.

Clinical safety

- Patient exposure

The main sources of safety data are derived from patients with PAH and hypertension treated with sildenafil 20, 40 and/or 80mg TID chronically in phase 2/3 studies. A total of 277 patients with PAH (70 placebo, 207 received sildenafil) were enrolled in the 12-week pivotal study A1481140; 259 of these 277 patients (94%) were subsequently enrolled in the ongoing open extension study A1491142 in which all patients were titrated to 80mg TID if tolerated. Given the proposed fixed sildenafil dosage of 20mg TID, these data yielded a considerable safety margin. At the time of the data cut of July 2004, the total patient exposure was 5 times higher in the extension compared to the pivotal study (236.2 vs. 47.8 pt-years, respectively) and a total of 149 out of 274 (54%) patients had been treated for ≥ 1 year, almost exclusively driven by patients titrated at 80mg TID.

Another main source of safety data are the 199 patients (60 placebo, 139 sildenafil) treated in the 4-week hypertension study A1481165.

No head-to-head comparison with active comparators has been made, precluding a direct comparison of the safety of sildenafil versus other PAH treatments such as bosentan.

- Adverse events

The overall proportion of subjects with common adverse events (AEs) in pivotal study A1481140 was similar across all treatment groups including placebo (~90%), which was also true for the proportion of subjects with severe AEs (~17%) and the number of AEs normalised to patient exposure.

Frequently encountered common AEs reported more often by sildenafil compared to placebo-treated patients included headache (45.9% vs. 38.6%, resp), flushing (11.6% vs. 4.3%), back pain (11.6% vs. 11.4%), dyspepsia (11.1% vs. 7.1%), diarrhoea (10.1% vs. 5.7%), pain in the limb (10.1% vs. 5.7%) and myalgia (9.2% vs. 4.3%). A markedly higher (difference >5%) incidence with sildenafil compared to placebo was observed for headache, flushing and epistaxis (6.8% vs. 1.4%). The incidence of individual severe AEs was below 3% in each sildenafil treatment group.

Myalgia, peripheral oedema, upper respiratory tract infection and visual disturbance showed some dose-dependency.

Several of these common AEs are already known to occur with sildenafil treatment in MED, but the rates are generally lower in MED patients on 25-100mg (as needed) compared to these chronically treated PAH patients on higher daily dosages.

Importantly, the disease-related severe AEs right ventricular failure, exacerbated dyspnoea and aggravated pulmonary hypertension were less frequently encountered in sildenafil compared to placebo.

In the extension study, the incidence of common and severe AEs increased compared to the pivotal study, but the rates normalised to sildenafil exposure were comparable or lower in the extension versus pivotal study, suggesting no excess AEs to develop during long-term sildenafil exposure. The incidences of the most frequently occurring severe AEs right ventricular failure and aggravated pulmonary hypertension in the extension study, compared favourably with the placebo group in the pivotal study (~3.3% vs. 4.3%, resp).

No cases of priapism were noted in either study.

In the healthier population of the hypertension study, differences in common AE incidences between sildenafil 20-80mg TID and placebo were more marked, but also concerned known sildenafil-associated AEs such as headache, flushing and dyspepsia.

- Serious adverse event/deaths/other significant events

Serious adverse events

In the pivotal study, the overall incidence of serious adverse events (SAEs) on sildenafil was lower as compared to placebo (14% vs. 18%, respectively), while no dose-dependency was noted in the sildenafil group.

Five SAEs occurred more frequently in sildenafil-treated patients compared to placebo: septic shock, upper respiratory tract infection, asthenia, oedema, and pyrexia at a frequency of 1% each.

The SAEs that occurred more frequently with placebo were pulmonary hypertension, chest pain, right ventricular failure, dyspnoea, cardiac failure and pneumonia. In contrast to the SAEs noted more frequently with sildenafil, most of the SAEs occurring more frequently with placebo are directly reflective of the progression of the underlying cardiopulmonary disease. Such a pattern was also noted for severe AEs (see above), and provides some reassurance regarding the cardiovascular safety of sildenafil in PAH patients.

In the extension study, the most frequently reported SAEs on sildenafil were right ventricular failure (5.0%), pulmonary hypertension (3.9%), and dyspnoea (3.9%). Similar to the common and severe AEs, these SAE incidences are higher as compared those noted in the pivotal study, but the rates per patient-year of exposure were rather comparable in the extension and pivotal study, again indicating

no excess to develop during long-term exposure. These data should however be interpreted with caution due to the limited number of patients treated with sildenafil for ≥ 1 year (n=149).

Deaths

The incidence of death in the pivotal study was similar in the placebo and the combined sildenafil group (1.4%), while no deaths were considered to be treatment related. The mortality rates normalised to exposure during the pivotal study or within 40 days of discontinuing this study, were comparable between sildenafil and placebo: 6.3 vs. 6.1 per 100 pt-years, resp. Across the pivotal and extension studies, most deaths were related to cardiopulmonary causes. In line with the results on SAEs, the proportion of patients that died in the extension study (15/259 = 5.8%) was considerably higher as compared to pivotal study. However, up to the data cutoff, the rate of death in the extension study or within 40 days of discontinuing the study was 5.9 per 100 pt-years and thereby comparable to the exposure normalised rate in the pivotal study. Thus, within the limitations posed by the low extent of sildenafil exposure and the infrequent nature of SAEs and death, it would appear as if no excess SAEs or deaths developed during long-term sildenafil exposure in the extension study compared to the medium-term exposure in the pivotal study, while a comparable death rate and a lower overall SAE rate was noted with sildenafil versus placebo in the pivotal study.

No deaths occurred in the short-term hypertension study.

Visual symptoms

Dose-dependent abnormal vision was observed with Viagra and is thought to be due to the effect of sildenafil on the PDE6 enzyme of retinal photoreceptors. In 2002, two meta-analyses reported that no consistent pattern had emerged to suggest any structural alterations to the visual system with long-term prn (as needed) dosing in MED patients.

In the chronic dosing pivotal PAH study, the most frequently encountered visual AEs with sildenafil were visual disturbance (3.9%), blurred vision (4.3%) and chromatopsia (2.4%), of which visual disturbance and chromatopsia were more frequently observed with sildenafil compared to placebo and showed some dose-dependency. This pattern of ophthalmic AEs bears similarities with Viagra. Blurred vision was also frequently reported in the placebo group (5.7%), suggesting a relationship with underlying pathology. In the extension study, the most frequently encountered ophthalmic AEs were blurred vision, visual disturbance, retinal haemorrhage, conjunctival- and episcleral hyperaemia, of which the latter two may be related to vasodilatation due to PDE5 inhibition. The incidences for ophthalmic AEs were higher in the extension study compared to the pivotal study, while the rates normalised to exposure were consistently lower in the extension versus the pivotal study (visual disturbance 0.06 vs. 0.17, blurred vision 0.09 vs. 0.19 events per pt-year of exposure, resp), again suggesting no excess ophthalmic AEs to develop during long-term exposure. No discontinuations were primarily due to ophthalmic symptoms, but ophthalmic symptoms were part of a symptom array leading to discontinuation in two patients.

Regarding the subjective performance tests on visual acuity, visual fields and contrast sensitivity in the pivotal study, the proportion of patients with deterioration from baseline was generally comparable in the 3 sildenafil treatment groups as compared to the placebo group at Week 12, while the proportion of patients with deterioration from study A1481140 baseline remained stable between Week 12 and 24. The Farnsworth Munsell D-15 tests did not indicate that sildenafil causes a specific colour vision defect at dosages up to 80mg TID in patients with PAH. Colour vision results obtained with a larger single dose of sildenafil (100 mg) in healthy volunteers have been incorporated in the SPC (section 5.1).

To date, no cases of non-arteritic ischaemic optic neuropathy (NAION) have been reported with sildenafil treatment in patients with PAH. Given the fact that series of case reports on NAION occurring in temporal relationship with the use of sildenafil in MED patients with atherosclerotic risk factors have been published in medical literature (Pomeranz et al. 2005; Howard et al. 2005), this serious adverse event should be specifically addressed in the Risk Management Plan.

Bleeding events

In the pivotal study, the overall incidence of bleeding events was comparable in the combined sildenafil and placebo group, but epistaxis was markedly more frequently noted in the sildenafil group compared to the placebo group (6.8% vs. 1.4%, resp). This increase was particularly evident in the CTD subpopulation. Most epistaxis events were of mild severity and self-limiting, while all events resolved. Also, an increased incidence of ophthalmic haemorrhage (retinal-, eye-, and conjunctival haemorrhage combined) was noted in sildenafil treated patients compared to placebo treated patients (3.9% vs. 1.4%, resp), without evidence for dose-dependency. Further analysis of these bleeding events, showed that these predominantly occurred in patients using concomitant vitamin K antagonists with a higher overall incidence in the sildenafil treatment group compared to placebo (20.3% vs. 12.5%, resp). In patients not using vitamin K antagonists, a lower frequency in the sildenafil versus placebo patients was noted. Two SAEs were reported in association with bleeding events during sildenafil treatment (epistaxis and hemorrhagic gastritis). In the extension study, the overall incidence of bleeding AEs was higher compared to the pivotal study (41% vs. 16%, resp) and also showed predominance of the AEs epistaxis (8.5%) and ophthalmic haemorrhage (8.8%). However, the rates normalised to patient exposure were lower in the extension versus pivotal study regarding epistaxis (0.09 vs. 0.29 per patient-year, respectively) and ophthalmic haemorrhage (0.10 vs. 0.15 per patient-year, respectively). As of September 2004, 12 patients (4.6%) have reported a total of 14 SAEs of bleeding in the extension study, most frequently haemoptysis and menorrhagia associated with the use of concomitant vitamin K antagonists.

- Laboratory findings

In the pivotal study, the number of patients with abnormal test results (normal baseline) was comparable in each treatment group. The most frequently observed abnormalities during the study were decreased lymphocytes and elevated total neutrophils, basophils and monocytes across all treatment groups including placebo. Liver function tests, creatinine, and electrolytes showed no apparent differences between the active treatment groups and placebo. In the extension study, again the most frequently noted abnormalities related to decreased lymphocytes and elevated total neutrophils, basophils and monocytes. The clinical relevance of these particular findings is unclear, but appears to be limited as no sildenafil-treated patient discontinued after randomisation due to a laboratory adverse event.

- Safety in special populations

Sildenafil-treated CTD patients reported more common AEs and SAEs compared to sildenafil treated PPH patients, suggesting a somewhat unfavourable impact of CTD aetiology on the sildenafil safety profile. The presence of hepatic impairment had a mild negative influence on the safety profile of sildenafil and placebo, but the low number of patients in the sildenafil group (n=17) precludes drawing any firm conclusions. No meaningful assessment of safety in PAH patients with renal insufficiency could be performed (n=3). Regarding gender, it appeared that females were more likely to experience AEs compared to male patients during sildenafil treatment, but AE rates in placebo and sildenafil-treated females were rather similar. There was no clear impact of age on the safety profile of sildenafil, although the low number of elderly patients treated with sildenafil (n=39) once again precludes drawing any conclusions. Given the low numbers of patients aged ≥65 years, a safety analysis for very elderly patients (≥75 years) was not expected to yield meaningful information.

- Safety related to drug-drug interactions and other interactions

See sections "*Pharmacodynamic interactions*" and "*Bleeding events*"

- Discontinuation due to adverse events

In the pivotal study, discontinuation rates were low and similar in the placebo and sildenafil 20mg TID group (2.9%), but progressively higher with sildenafil 40 and 80mg TID (4.5% and 8.5%, resp). A total of 37 patients (14%) discontinued during the subsequent extension study, representing a lower

sildenafil discontinuation rate normalised to exposure in the extension versus pivotal study (0.16 vs. 0.23 per pt-year, resp). A substantial proportion of these discontinued due to death. Most other discontinuations were related to AEs, without any predominate cause.

- Post marketing experience

Relevant Viagra data are discussed in previous sections

- Discussion on clinical safety

The most commonly reported adverse reactions that occurred (greater or equal to 10 %) on Revatio compared to placebo were headache, flushing, dyspepsia, back pain, diarrhoea and limb pain. As for Viagra, eye disorders were reported.

The poor prognosis of the disease and the lack of a control group make it difficult to draw conclusions about the causality of deaths in the extension study. An exploratory 1-year sildenafil survival analysis with historical comparisons in the subset of PPH patients only, suggested that mortality rates with sildenafil are in line bosentan and epoprostenol, thereby not posing a safety concern. However, further data are necessary.

Overall, data indicate that sildenafil increases the risk of bleeding events, but only in the presence of concomitant vitamin K antagonists, which are frequently used by PAH patients. The observed events of epistaxis may be related to enhanced blood flow to the nasal turbinates during sildenafil treatment. The exact underlying mechanism regarding ophthalmic bleeding with sildenafil is less clear, but may be related to vasodilatation as well. No interactions were seen between sildenafil and anticoagulants in the MED development program. In the absence of a clear mechanistic explanation, no reassurance exists that this apparently increased bleeding tendency would not extend to more serious bleeding events such as cerebrovascular haemorrhage. Given the infrequent nature of serious bleeding events and the limited number of sildenafil-treated CTD patients included in the studies (n=62), the trial programme could be expected to lack statistical power for elucidating clinically important differences in serious bleeding events. 'Epistaxis and other bleeding events' is therefore defined as a safety risk in the Risk Management Plan.

To address safety risks, a Risk Management Plan is planned.

Epistaxis and other bleeding events, cardiovascular safety, hypotension, long-term mortality, ocular safety (including NAION), safety data in PAH patients co-prescribed sildenafil with approved therapies (e.g. epoprostenol or bosentan), and data in patients with severe renal impairment, in the paediatric population and in pregnant women have been defined as clinical safety specifications i.e. potential risks or missing data. As part of Non-clinical safety specifications, the need for further non-clinical studies to gather information about the underlying mechanisms for which sildenafil may produce NAION and other vascular and non-vascular effects in the eye, will be evaluated.

Planned actions mainly consist of enhanced pharmacovigilance and safety assessment in ongoing (extension studies A1481142 [sildenafil only] and A1481153[sildenafil-epoprostenol]) and planned clinical studies (co-adminstration with bosentan). In addition, a natural history study is proposed to better understand the natural history of bleeding in the PAH population. For the enhanced pharmacovigilance, PSUR is listed as milestone.

Data on interactions should be obtained through the safety and efficacy study of the co-administration of sildenafil and bosentan.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

Non-clinical pharmacology and toxicology

Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Pharmacodynamic data suggested that it could relax pulmonary vascular smooth muscle, prevent in the presence of NO platelet-based obstructions to blood flow and relax peripheral blood vessels. Several possible adverse events (vasodilatation, antidiuretic effect, haemorrhagic risk, inhibition of gastric emptying and visual disorder) can be associated with the use of sildenafil in view of its pharmacological profile.

Efficacy

Based on the pivotal trial, sildenafil has shown a statistically significant effect on exercise capacity (placebo corrected improvement of exercise capacity of 45.3 meters with sildenafil 20 mg TID) in patients treated over 12 weeks. Consistent with this the percentage of subjects on sildenafil who reached an improvement of at least one functional class was greater than with placebo. The effect was not clearly shown to be dose-dependent.

The effect of sildenafil on other variables, including survival and clinical variables (e.g. dyspnoea) are limited and only considered descriptive. Further data will be expected on mortality.

Safety

In general, sildenafil seems to be well tolerated in PAH patients having a safety profile consistent with that of sildenafil in the MED population.

Nevertheless, several potential risks or missing data should be further assessed in a risk management plan; they include bleeding events, cardiovascular safety, long-term mortality, ocular safety, co-administration with other PAH treatments.

Benefit/risk assessment

In a population of patients with idiopathic and CTD-associated PAH treated with conventional therapy, sildenafil 20mg TID has been shown to yield a statistically significant and clinically relevant improvement in exercise capacity, as reflected in a mean placebo-corrected improvement in 6-Minute Walk Test distance of approximately 45 meters after 12 weeks. It is of note that no head-to-head comparison with other PAH treatments such as bosentan and iloprost has been made, and that no (placebo-controlled) data are currently available on main clinical endpoints showing the efficacy of sildenafil op top of these non-conventional PAH treatments.

The limited amount of patients included in clinical trial programme for this orphan drug application, mainly impacts on the safety assessment as these studies had low power to elucidate potential clinically relevant differences in the occurrence of less frequent events, such as serious adverse events and deaths. Although the rates of death and serious adverse events with sildenafil relative to placebo raised no safety concern, an effect of mortality has not been established. The poor prognosis of the disease and the lack of a control group make it difficult to draw conclusions on the causality of deaths observed in the long-term extension study. The applicant committed to provide further mortality data in the future on the basis of ongoing studies with discussion in the context of historical survival data.

Safety concerns exist regarding the occurrence of bleeding events and visual symptoms, both of which have been incorporated in the Risk Management Plan.

As stated earlier, a direct comparison with other non-conventional PAH treatments has not been made, but the improvement in exercise capacity obtained appears to be in line with other recently authorised PAH treatments.

In view of inconvenience with regard to safety and/or mode of administration of authorised products in PAH, the benefit risk of sildenafil is positive, as it may offer physicians a valuable alternative treatment option in this devastating, incurable condition.

Overall, considering that the indications for which Revatio is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the safety and efficacy, Revatio should be granted a marketing authorisation under exceptional circumstances. Further data on mortality and safety will have to be provided as specific obligations.

Similarity with authorised orphan medicinal products

The claimed indication of Revatio significantly overlaps with the indications granted to two EU authorised orphan medicinal products; Tracleer (bosentan) and Ventavis (iloprost). Considering however that both the principal molecular structural feature and mechanism of action of sildenafil differ from those of both bosentan and iloprost, the CHMP is of the opinion that Revatio does not contain a similar active substance (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Tracleer or Ventavis, and thus cannot be considered to be similar to either of those medicinal products within the meaning of that Article 3.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Revatio in the following indication: “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” was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Revatio not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to authorised orphan medicinal products for the same therapeutic indication.