CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	11/12/2009
From	Mehul Mehta, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-473
Applicant	Pfizer
Date of Submission	12/16/08 (PDUFA fee received 1/21/09)
PDUFA Goal Date	11/21/09 (Saturday)
Proprietary Name / Established (USAN) names	Revatio Injection (sildenafil citrate)
Dosage forms / Strength	Sterile solution (injection) / 0.8 mg/ml
Proposed Indication(s)	For the continued treatment of patients who are currently prescribed oral Revatio and who are temporarily unable to take oral medication.
Recommended:	*Approval*

1. Introduction and Background

The following disciplines conducted a review for this submission:

Clinical – primary reviewer Dr. Maryann Gordon; secondary reviewer – Dr. Shari Targum; primary and secondary sign-off in DAARTS on 10/28/09.
Clinical Pharmacology – primary reviewers Drs. Satjit Brar and Ping Zhao; secondary reviewers – Drs. Jadhav and Madabushi; primary and secondary sign-off in DAARTS on 10/16/09.
Pharm/tox – primary reviewer Dr. Thomas Papoian; sign-off in DAARTS 02/24/09.
Chemistry – primary reviewer - Dr. Mohan Sapru; secondary reviewer – Dr. Ramesh Sood; primary and secondary sign-off in DAARTS on 11/16/09.
Microbiology – primary reviewer Dr. Langille; secondary reviewer Dr. Mcvey; primary and secondary sign-off in DAARTS on 10/23/09

As stated in Dr. Gordon's review:

"Pfizer, the sponsor of NDA #22473, REVATIO [redacted] injection, is seeking approval for the treatment of adult patients with Pulmonary Arterial Hypertension (PAH) who are temporarily unable to take oral medication, and for whom the physician believes continuity of treatment is in the patient's best interest. b(4)

Sildenafil tablet was originally approved in 1998 for the treatment of male erectile dysfunction under the trade name Viagra® (NDA 20-895). The sildenafil tablet was approved in 2005 to improve exercise ability in patients with PAH. Recently, the indication was expanded to

include the delay in clinical worsening in the same patient population. Had the sponsor not pursued the additional claim of clinical worsening, there would be no consideration by the Agency for an IV formulation.

The sponsor proposes that intravenous sildenafil is desirable in circumstances where short term interruption of oral sildenafil is necessary and the physician decides that continuation of therapy is in the best interest of the patient. The sponsor is not claiming, nor would the Agency agree, that short term interruption of oral therapy results in immediate and rapid worsening of symptoms of PAH in otherwise stable patients. However, there are instances when a patient with PAH cannot receive oral administration of sildenafil and maintaining therapeutic levels of Sildenafil is likely to be important in maintaining the progression effect, even if the effect on exercise cannot be appreciated.

The Agency has agreed with the sponsor regarding the following principles:

-Oral sildenafil is effective in reducing the incidence of clinical worsening events.
-Clinical deteriorations are often very difficult to reverse in PAH (Naeje 2007 *Exp Opin Pharmacoth*).
-The data suggest that maintenance of Revatio therapy is important in managing disease progression in PAH.
-The availability of IV formulation would give the physicians the ability to maintain treatment with Revatio in patients temporarily unable to take oral formulation.
-The strategy to select an IV dose based on PK modeling referencing the approved oral dose is acceptable.
-While it is desirable to conduct an efficacy trial in hospitalized PAH patients, it is probably not possible."

2. CMC/Device

The following information is obtained from the 11/09/09 review of Drs. Sapru and Sood.

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, this NDA for Revatio® (Sildenafil) Injection (for intravenous use) is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

3. Nonclinical Pharmacology/Toxicology

The following information is obtained from the 02/24/09 review of Dr. Papoian.

"**1.1. SUBMISSION BACKGROUND**

Oral administration of sildenafil citrate has been approved previously for the indications of male erectile dysfunction (Viagra→; NDA #20-895) and pulmonary hypertension (Revatio→; NDA #21-845). The current application (NDA #22-473) is to gain approval of Revatio→ (sildenafil citrate) for intravenous (i.v.) use in adult patients with pulmonary arterial hypertension (PAH) who are temporarily unable to take oral medication, and for whom the physician believes continuity of treatment is in the patient's best interest. This application represents a new pharmaceutical formulation, strength, and route of administration for sildenafil citrate.

According to the sponsor, an i.v. dose of 10 mg t.i.d. (i.e., 3X/day) over 5 min to humans is projected to produce a similar AUC (i.e., systemic exposure) to that following the recommended therapeutic oral dose of 20 mg t.i.d.

Although no new pharmacology or toxicology studies were conducted or submitted with this application, previous nonclinical studies submitted in support of NDAs #20-895 (Viagra→) and #21-845 (Revatio→) were used to support the safety of the new i.v. formulation.

1.2. RECOMMENDATIONS

1.1.1. Recommendation on Approvability

Approvable

1.1.2. Recommendations for Additional Nonclinical Studies
None

1.1.3. Recommendations on Labeling

None"

4. Clinical Pharmacology/Biopharmaceutics

The 10/16/09 review from OCP (Drs. Jadhav, Zhao and Madabushi) states the following:

"1. EXECUTIVE SUMMARY:

"The clinical pharmacology studies referenced in this application were originally submitted under NDA 20-895 [Viagra®] and NDA 21-845 [Revatio®]. The original packages included characterization of single dose and multiple dose pharmacokinetics, ADME characteristics,

bioavailability and bioequivalence studies, potential interactions with other medications, and studies in special populations, including pharmacokinetic evaluation of sildenafil citrate in patients with PAH. The current package includes resubmission of relevant data to justify a dosing recommendation for IV sildenafil citrate.

No new clinical studies have been submitted. The clinical pharmacology program for NDA 22-473 references a total of 5 clinical studies incorporating the use of IV and oral formulations of Sildenafil citrate in healthy volunteers and PAH patients (study 148-203, 148-208, 148-215, 148- 301, and A1481024). The package includes a population pharmacokinetic study which evaluates the absolute bioavailability of oral sildenafil citrate. It also includes simulations along with external validation to justify dosing.

The following are the major findings:

1. The absolute bioavailability of sildenafil is approximately 40%. Therefore, 8 mg IV dose of sildenafil is reasonable to match AUC (of parent drug only) after IV and 20 mg oral dose.

2. The 10 mg IV dose has been selected to yield similar total PDE5 inhibition from sildenafil and the major active metabolite, UK-103,320, to that observed with a 20 mg oral dose.

3. The drug interaction potential with CYP inhibitors is likely to be lower. Therefore, the sponsor's labeling claim is acceptable.

1.1 RECOMMENDATION:

The Office of Clinical Pharmacology has reviewed the information submitted under NDA 22-473 for sildenafil (Revatio® Injection) and finds the sponsor's dosing rationale acceptable. We recommend approval of Revatio® Injectior [redacted] b(4)

1.2 PHASE IV COMMITMENTS:

Not Applicable"

2. Summary of OCP Findings

The proposed dose for sildenafil citrate IV injection is 10 mg three times a day (TID) given as a bolus injection. This dose is expected to yield similar total PDE5 inhibition from the plasma concentration of sildenafil plus the major active metabolite, UK- 103,320, to that observed with a 20 mg TID oral dose (the current recommended oral therapeutic dose for patients with PAH).

Sildenafil PK parameters were obtained from a combined population analysis of pharmacokinetic data from healthy volunteers in three studies (study 148-203, 148-208 and 148- 215, oral and IV formulation). In these studies sildenafil IV and oral doses were studied (see Table 1). The PK profile of a 10 mg intravenous bolus dose of sildenafil was simulated

based on healthy patient PK parameters. It is important to note that a study involving administration of a 10 mg IV bolus has not be performed in healthy or PAH patients.

The clinical pharmacology review focused on the following key questions:

Does a 10 mg IV bolus dose of sildenafil provide an equivalent exposure to 20 mg PO dose?
The 10 mg IV bolus does not provide an equivalent exposure to 20 mg oral dose (PO) for the parent compound, sildenafil. The Cmax observed after 10 mg IV administration is >2 fold higher than that from 20 mg PO. The AUC after 10 mg IV bolus is 1.4-fold higher than that from 20 mg PO dose yielding an exposure of 338 and 240 h·ng/ml, respectively. To achieve a similar plasma sildenafil exposure (AUC) as observed for 20 mg sildenafil administered orally, the required IV dose is calculated to be 8 mg (~40% bioavailability estimated from two sources).

Is the strategy used to derive dosing recommendation, accounting for the active metabolite, appropriate for PAH patients?
Yes, the strategy accounting for active metabolite is acceptable. The strategy used for dosing recommendation matches total (parent + active metabolite) PDE5 inhibition after oral and IV administration. The circulating concentration of the major metabolite, UK-103,320, observed following IV administration is lower than for oral dosing (14.4% of parent vs. 54% of parent; taken from study 148-215). This active metabolite has been shown to have PDE5 inhibitory activity, with 50% of the potency of sildenafil.

Do the PK characteristics of sildenafil translate from healthy volunteers to PAH patients?
Yes. External validation was performed with a population PK model (generated from healthy individuals), and compared to observed concentrations in PAH patients for the oral and IV formulations. The population model that accounts for 30% difference in clearance between healthy volunteer and PAH patients predicts exposures in PAH patients (by ~30%).

Is the dose of 10 mg TID appropriate for PAH patients?
Yes. The plasma concentrations of parent drug will be higher by 2.0 fold after the proposed IV dose compared to the approved oral dose. The efficacy of 10 mg IV is expected to yield a similar PDE5 inhibition to 20 mg PO, accounting for sildenafil and active metabolite. Moreover, there is sufficient safety experience for sildenafil at exposures significantly higher than that of the proposed IV dose. The expected exposures after 10 mg IV bolus is much lower than that observed in both healthy volunteers and PAH patients receiving higher doses as an infusion or oral preparation, which were well tolerated.

Is the sponsor's labeling claim on lower drug interaction potential between sildenafil and CYP3A inhibitors following IV administration compared to PO administration reasonable?
Yes, from mechanistic viewpoint the sponsor's claim is reasonable. Further, drug interaction potential with the IV sildenafil formulation was assessed via simulation with SimCYP©. The pharmacokinetics of sildenafil after IV (50mg or 80mg) or PO (50 mg or 100mg) administration was assessed after co-administration with ketoconazole or ritonavir (CYP3A

inhibitors) using simulations. There were some limitations identified (see Dr. Ping Zhao's review on DDI Interaction Simulations with SimCYP®) in the sponsor's analysis. Therefore, while the claim is acceptable, we are not recommending any quantitative information in the label.

5. Clinical Microbiology

The following information is obtained from the 10/23/09 review of Drs. Langille and Mcvey.

"I. Recommendations

A. Recommendation on Approvability -

NDA ——— is recommended for approval from the standpoint of product quality microbiology. b(4)

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The drug product is passed through ——— and ——— b(4)

B. Brief Description of Microbiology Deficiencies -

No deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies –

Not applicable"

6. Clinical/Statistical- Efficacy

Dr. Gordon's review of 10/28/09 states the following:

"In conclusion,

- The information supplied from NDA #22473 provides enough evidence that an IV bolus dose of 10mg TID will be safe and effective.

- There is sufficient safety experience for sildenafil at exposures significantly higher than that being currently proposed of the approval of IV formulation. Because of the short half life of both sildenafil and the active metabolite UK-103,320 (~4 hours for both) no accumulation of either sildenafil or its metabolites is expected during TID intravenous dosing.

- The adverse event profile for IV sildenafil in adults with PAH was consistent with the adverse event profile for marketed oral Revatio® in adults with PAH. The expected exposures after 10 mg IV bolus is much lower than that observed in both healthy volunteers and PAH patients receiving higher doses as an infusion or oral preparation, which were well tolerated. Therefore, there are no expected safety concerns.

- Based on previous experience for Revatio® in patients with PAH, the efficacy is expected to be similar between 20 mg PO and the proposed 10 mg IV administration.

- The inherent pharmacokinetic differences between oral and IV sildenafil have been evaluated in two separate studies with healthy patients. The estimated bioavailability of the oral formulation has been assessed at the 50 mg oral dose. The estimated bioavailability at this dose level is estimated to be 41% which is similar to that found in the Muirhead reference (~38%). It is also noted that the extent of formation of the active metabolite (UK-103,320) differs between IV and oral formulations. The dose of 10 mg TID given as a bolus injection has been selected to yield similar PDE5 inhibition from total plasma concentration of sildenafil *plus* the major active metabolite UK-103,320 to that observed with a 20 mg TID oral dose. Specifically, the IV dose calculated to yield similar total plasma concentrations of [sildenafil + UK-103,320] for an oral 20 mg dose is 9.82 mg, rounded to 10 mg for use in clinical practice. This comparison includes adjustment for the bioavailability, and both relative potency and protein binding of both sildenafil and the active metabolite UK-103,320. According to the Clinical Pharmacology reviewer, this approach is deemed appropriate for dose selection.

- The sponsors are not requesting the IV formulation to be used for long term use.

- The sponsor has demonstrated a clinically and statistically significant effect on the delay in clinical worsening of PAH using the oral formulation. Intravenous

Revatio® provides an alternative treatment formulation for the PAH population that is unable to take medications orally as it provides similar exposure to the active moieties.

- Based on the understanding of the metabolic pathway of sildenafil, any drug interactions with other drugs after IV administration of sildenafil should be less than that after oral administration. Data suggest that sildenafil is metabolized by CYP3A4 in the gut as well as the liver. Predictions based on a pharmacokinetic model suggest that drug-drug interactions with CYP3A4 inhibitors should be less than those observed after oral sildenafil administration. The magnitude of the interaction is expected to be reduced for IV sildenafil, as interactions for oral sildenafil are due, at least in part, to effects on oral first pass metabolism.

- Founded on the wide safety margin for sildenafil and the fact that exposures of sildenafil between the 10 mg IV and 20 mg oral formulations are expected to be similar, switching between formulations should not result in safety issues or lack of efficacy. This is the expectation upon switching formulations in either direction (i.e., oral to IV or IV to oral) during patient hospitalization.

Recommendation on Regulatory Action

Approval

Recommendation on Post marketing Actions

None"

7. Safety

Dr. Gordon's review of 10/28/09 states the following:

"2.7.4.1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies
The safety and efficacy of sildenafil citrate has been extensively investigated in the original male erectile dysfunction (MED) development program, including 31 Phase 2/3 clinical trials and 35 clinical pharmacology studies, and over 4,500 subjects that received sildenafil (NDA 20-895). Since approval of sildenafil for MED, over 35 million patients have received sildenafil for the treatment of MED.

The safety profile of REVATIO oral tablets has been previously established in adults with PAH. The database has previously been submitted (NDA 21-845) to support the safety of the oral formulation for PAH, and an overview of this data is given below.

The remainder of this document presents safety data from seven studies involving intravenous sildenafil. All of the seven studies utilizing IV sildenafil citrate were conducted as part of the original sildenafil citrate submission for the treatment of MED (VIAGRA) [NDA 20-895] with

the exception of studies A1481024, A1481134 and A1481157, which were included in the original REVATIO submission (NDA 21-845).

SAFETY REVIEW

...the proposed dose is 10 mg (12.5 ml) three times a day (TID) given as a bolus injection. The IV dose was selected because it yielded similar PDE5 inhibition to that obtained with the approved oral dose (20 mg TID) for PAH patients.

This summary document supports the safety of REVATIO [redacted] injection 10 mg TID in patients with PAH. b(4)

Based on a evaluation by the sponsor of available safety data with a worldwide data cutoff date of July 31, 2008, the results support the following conclusions:

- The adverse event profile for intravenous sildenafil in adults with PAH is consistent with the adverse event profile for marketed oral REVATIO in adults with PAH.

- Intravenous sildenafil is safe and generally well tolerated at all doses studied in patients with PAH.
- As expected with inhibition of PDE5 and in line with the accumulated knowledge of sildenafil, the most common adverse events reported were headache, hypotension, vasodilatation, and dizziness."

8. Advisory Committee Meeting

An AC was not held for this NDA.

9. Pediatrics

Pediatric age group(s) to be waived. Ages 0-16 years
Reason for waiving pediatric assessment requirements:
Studies are impossible or highly impractical (e.g., the number of pediatric patients is so small or is geographically dispersed).

10. Other Relevant Regulatory Issues

None.

11. Labeling

FDA sent the sponsor the draft package insert for review – emailed 11/9/09. In correspondence dated October 22, 2009, FDA asked the sponsor to change the product name from [redacted] to Revatio (sildenafil) Injection. b(4)
Final labeling to be determined.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:

After going over the reviews of all the team members, I concur with the recommendations of the team, particularly the opinions of the clinical pharmacology and clinical reviewers, i.e., I recommend approval of this submission.

The basis behind my recommendation for approval is:

Regimen of 20 mg t.i.d. oral sildenafil has been shown to be efficacious in treatment of PAH. Recently, this regimen has received 'delay in worsening' claim for this indication. This subsequently has led to the consideration for the need for an IV formulation for temporary use in patients on oral therapy who cannot take the drug orally for a limited period.

Clinical pharmacology review has shown that based on the absolute bioavailability estimates and PDE5 inhibition by the parent drug and the active metabolite via the IV and the oral routes, 10 mg IV dose provides comparable inhibition as the 20 mg oral dose. Thus 10 mg t.i.d. IV dosing is expected to show comparable efficacy to that shown by the 20 mg t.i.d. oral dosing.

The clinical and clinical pharmacology reviews show that even though the 10 mg IV dose will result in higher (by 2 fold) Cmax of sildenafil, acceptable safety has been demonstrated based on the following:

1. The oral formulation of sildenafil has been studied to a maximum of 800 mg in healthy volunteers (single dose) and 80 mg three times a day (TID) in patients with PAH (average Cmax achieved was 5834 ng/ml).

2. The IV formulation as a single dose has been studied up to the 80 mg dose level in healthy volunteers and 40 mg as a single dose in patients with ischemic heart disease with no significant or unexpected adverse events.

3. In patients with PAH, target concentrations ranging from 100 ng/ml to 500 ng/ml have been evaluated from IV infusion (cumulative doses administered correspond to 5.75 mg over 20 minutes to 34 mg over 60 minutes, respectively). During this study the observed mean steady state plasma sildenafil concentrations were 128 (range 57.9-332), and 768 (range 398-2479) ng/mL, respectively. The maximum infusion rate administered to these patients was 11mg/5min.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22473	ORIG-1	PFIZER INC	REVATIO

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/s/

DANIEL BRUM
11/13/2009

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11/13/2009