CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021845Orig1s025

Trade Name:	Revatio
Generic or Proper Name:	sildenafil citrate
Sponsor:	Viatris Specialty LLC
Approval Date:	January 31, 2023
Indication:	The treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in pediatric patients (1 to 17 years old) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 021845/S-025

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Viatris Specialty LLC
Attention: Shan Lu, PhD, RAC
Regulatory Strategist Director
3711 Collins Ferry Road
Morgantown, WV 26506

Dear Dr. Lu:

Please refer to your supplemental new drug application (sNDA) dated and received March 31, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Revatio (sildenafil citrate) tablets.

This Prior Approval supplemental new drug application provides for a new indication: the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in pediatric patients (1 to 17 years old) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise.

This Prior Approval supplemental application also contains the final report for the following postmarketing requirement listed in the June 7, 2013 postapproval postmarketing requirement letter.

2026-1 Conduct a tial to investigate the effects on mortality of multiple doses of sildenafil in adults with pulmonary arterial hypertension.

Final Protocol Submission:	September 2013
Interim Report Submission:	July 2014 July 2015 July 2016 July 2017 July 2018 July 2019 July 2020 July 2021
Trial Completion:	July 2022

Final Report Submission: December 2022

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our June 7, 2013, letter. You are not required to report on the status of closed (released or fulfilled) PMRs in your annual report required under 21 CFR**:** 314.81 (b)(2)(vii).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Brian Cooney, Regulatory Project Manager, at (301) 796-0886.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REVATIO safely and effectively. See full prescribing information for REVATIO.

REVATIO (sildenafil) tablets, for oral use
REVATIO (sildenafil) for oral suspension
REVATIO (sildenafil) injection, for intravenous use
Initial U.S. Approval: 1998

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	1/2023
Dosage and Administration (2.1, 2.2, 2.3)	1/2023

---------- INDICATIONS AND USAGE----------

Adults
REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening. (1)

Pediatric Patients (1 to17 years old)
REVATIO is indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise (1, 14)

----------DOSAGE AND ADMINISTRATION----------

- Adults: 20 mg three times a day Dose may be increased based on symptoms and tolerability. (2 1)
- Pediatric patients (2.2)
  - ≤20 kg: 10 mg three times a day
  - 20 kg to 45 kg: 20 mg three times a day
  - >45 kg: 20 mg three times a day. Dose may be increased based on symptoms and tolerability.
- Injection (Adults): 10 mg three times a day administered as an intravenous bolus injection. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

- Tablets: 20 mg (3)
- For oral suspension: 10 mg/mL (when reconstituted) (3)
- Injection: 10 mg/12.5 mL in a single use vial (3)

---------- CONTRAINDICATIONS ----------

- Use with organic nitrates or riociguat. (4)
- History of hypersensitivity reaction to sildenafil or any component of the tablet, injection, or oral suspension. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Vasodilation effects may be more common in patients with hypotension or on antihypertensive therapy. (5.1)
- Use in pulmonary veno-occlusive disease (PVOD) may cause pulmonary edema and is not recommended. (5.2)
- Hearing or visual impairment: Seek medical attention if sudden decrease or loss of vision or hearing occurs. (5.4, 5.5)
- Pulmonary hypertension (PH) secondary to sickle cell disease: REVATIO may cause serious vaso-occlusive crises. (5.8)

---------- ADVERSE REACTIONS ----------

Adults: Headache, dyspepsia, flushing, pain in limb, myalgia, back pain and diarrhea. (6.1, 6.2)

Children: Priapism. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Viatris at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Use with strong CYP3A inhibitors: Not recommended. (7, 12.3)
- Concomitant PDE-5 inhibitors: Avoid use with Viagra® or other PDE-5 inhibitors. (5.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Adults

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening *[see Clinical Studies (14)]*.

Pediatric Patients (1 to 17 Years old)

REVATIO is indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standardized exercise testing, pulmonary hemodynamics thought to underly improvements in exercise *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults

Oral Dosage

The recommended dosage of REVATIO is 20 mg three times a day. Dose may be titrated to a maximum of 80 mg three times a day, if required, based on symptoms and tolerability *[see Clinical Studies (14)]*.

Although dose-response improvement in exercise ability was not observed in short-term studies in adults with PAH, the delay in clinical worsening with long-term use of sildenafil in Study A1481324 supports dosing up to a maximum of 80 mg three times a day *[see Clinical Studies (14)]*.

Intravenous Dosage

The recommended dose is 10 mg administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight.

A 10-mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20-mg oral dose.

2.2 Recommended Dosage in Pediatric Patients

Oral Dosage

The recommended dosage in patients ≤20 kg is 10 mg three times a day.

For pediatric patients 20 kg to 45 kg, the recommended dosage is 20 mg three times a day.

For pediatric patients 45 kg and greater, the recommended dosage is 20 mg three times a day. A maximum dose in pediatric patients has not been identified. Based on the experience in adults, dose may be titrated to a maximum of 40 mg three times a day for pediatric patients >45 kg, if required, based on symptoms and tolerability *[see Clinical Studies (14)]*.

2.3 Reconstitution of the Powder for Oral Suspension

Note: Reconstitute the contents of the bottle with a total volume of 90 mL (60 mL followed by 30 mL). Refer to the detailed instructions below.

1. Tap the bottle to loosen the powder.
2. Add 60 mL of water to the bottle.
3. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds.
4. Add another 30 mL of water to the bottle.
5. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds.
6. Remove cap and press the bottle adaptor into the neck of the bottle. Replace the cap on the bottle.
7. Write the expiration date of the reconstituted oral suspension on the bottle label (the expiration date of the reconstituted oral suspension is 60 days from the date of reconstitution).

Incompatibilities

Do not mix with any other medication or additional flavoring agent.

3 DOSAGE FORMS AND STRENGTHS

REVATIO Tablets

White, film-coated, round tablets engraved with “RVT20” containing sildenafil citrate equivalent to 20 mg of sildenafil.

REVATIO for Oral Suspension

White to off-white powders containing 1.57 g of sildenafil citrate (equivalent to 1.12 g of sildenafil) in a bottle for reconstitution to 10 mg/mL. Following reconstitution with 90 mL of water, the total volume of the oral suspension is 112 mL. A 2-mL oral dosing syringe (with 0.5 mL and 2 mL dose markings) and a press-in bottle adaptor are also provided.

REVATIO Injection

Single use vial containing 10 mg/12.5 mL of sildenafil.

4 CONTRAINDICATIONS

REVATIO is contraindicated in patients with:

- Concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions (5.1)]*.

- Concomitant use of riociguat, a guanylate cyclase stimulator. Phosphodiesterase-5 (PDE-5) inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

- Known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [blood pressure less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

5.2 Worsening Pulmonary Vascular Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

5.3 Epistaxis

The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

5.4 Visual Loss

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported post marketing in temporal association with the use of PDE-5 inhibitors, including sildenafil. Most

patients had underlying anatomic or vascular risk factors for developing NAION, including low cup to disc ratio ("crowded disc").

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority of whom have genetic disorders of retinal phosphodiesterases. Therefore, use of REVATIO in patients with retinitis pigmentosa is not recommended.

5.5 Hearing Loss

Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

5.6 Combination with Other PDE-5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

5.7 Priapism

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

5.8 Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Disease

In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PH secondary to sickle cell disease has not been established.

6 ADVERSE REACTIONS

The following serious adverse events are discussed elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions (5.1)]*
- Vision Loss *[see Warnings and Precautions (5.4)]*
- Hearing Loss *[see Warnings and Precautions (5.5)]*
- Priapism *[see Warnings and Precautions (5.7)]*
- Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Disease *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week, placebo-controlled clinical study and an open-label extension study (SUPER-1) in 277 REVATIO-treated adults with PAH (WHO Group I) *[see Clinical Studies (14)]* the adverse reactions that were reported by at least 10% of REVATIO-treated patients in any dosing group, and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature. The overall frequency of discontinuation in REVATIO-treated patients was 3% (20 mg and 40 mg three times a day) and 8% (80 mg three times a day). The overall frequency of discontinuation for placebo was 3%.

Table 1. Most Common Adverse Reactions in Patients Treated with REVATIO 20 mg, 40 mg, 80 mg and Placebo three times per day in SUPER-1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients)

	REVATIO 20 mg (n = 69)	**REVATIO 40 mg (n = 67)**	**REVATIO 80 mg (n = 71)**	**Placebo (n = 70)**
Headache	46%	42%	49%	39%
Flushing	10%	9%	16%	4%
Pain in Limb	7%	15%	9%	6%
Myalgia	7%	6%	14%	4%
Back Pain	13%	13%	9%	11%
Dyspepsia	13%	8%	13%	7%
Diarrhea	9%	12%	10%	6%

In a placebo-controlled fixed dose titration study (PACES-1) of REVATIO (starting with recommended dose of 20 mg and increased to 40 mg and then 80 mg all three times a day) as an adjunct to intravenous epoprostenol in patients with PAH, no new safety issues were identified except for edema, which occurred in 25% of subjects in the combined REVATIO + epoprostenol group compared with 13% of subjects in the epoprostenol group *[see Clinical Studies (14)]*.

In a study to assess the effects of multiple doses of REVATIO on mortality in adults with PAH (StudyA1481324), the lower dose 5 mg TID group showed a higher observed number of deaths (all related to underlying disease/disease under study), serious adverse events, and severe adverse events than the 20 mg and 80 mg TID groups *[see Clinical Studies (14)]*. Overall, the safety data for sildenafil 80 mg TID dose in Study A1481324 was consistent with the established safety profile of sildenafil in previous adult PAH studies.

Pediatric Patients

REVATIO was studied in a total of 234 PAH pediatric patients 1 to 17 years of age in a 16-week, double-blind placebo-controlled study (STARTS-1); 220 patients continued in a long-term extension study (STARTS-2). Erection increased was observed in 9% of patients treated with sildenafil in STARTS-1. No other new adverse reactions were identified in pediatric patients *[see Use in Specific Populations (8.4)]*.

REVATIO Injection

Adverse events with REVATIO injection were similar to those seen with oral tablets.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous System

Seizure, seizure recurrence

Ophthalmologic

NAION *[see Warnings and Precautions (5.4), Patient Counseling Information (17)]*.

7 DRUG INTERACTIONS

Nitrates
Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications (4)]*.

Strong CYP3A Inhibitors
Concomitant use of REVATIO with strong CYP3A inhibitors is not recommended *[see Clinical Pharmacology (12.3)]*.

Moderate-to-Strong CYP3A Inducers
Concomitant use of REVATIO with moderate-to-strong CYP3A inducers (such as bosentan) decreases the sildenafil exposure. Dose up-titration of REVATIO may be needed when initiating treatment with moderate-to-strong CYP3A inducers. Reduce the dose of REVATIO to 20 mg three times a day when discontinuing treatment with moderate-to-strong CYP3A inducers *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Limited published data from randomized controlled trials, case-controlled trials, and case series do not report a clear association with sildenafil and major birth defects, miscarriage, or adverse maternal or fetal outcomes when sildenafil is used during pregnancy. There are risks to the mother and fetus from untreated pulmonary arterial hypertension *(see Clinical Considerations).* Animal reproduction studies conducted with sildenafil showed no evidence of embryo-fetal toxicity or teratogenicity at doses up to 32- and 65-times the recommended human dose (RHD) of 20 mg three times a day in rats and rabbits, respectively *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women with untreated pulmonary arterial hypertension are at risk for heart failure, stroke, preterm delivery, and maternal and fetal death.

Data

Animal Data

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 65-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of REVATIO to an infant during lactation.

8.4 Pediatric Use

The safety and efficacy of REVATIO have been established in pediatric patients 1 to 17 years old, for the treatment of PAH (WHO Group I) to improve exercise ability and, in patients too young to perform standard exercising testing, pulmonary hemodynamics thought to underly improvements in exercise Use of REVATIO for this indication is supported by evidence from adequate and well-controlled studies in adults with additional PK and safety data in pediatric patients aged 1 year and older *[see Adverse Reactions (6.1), Clinical Studies (14)]*. The safety and effectiveness of REVATIO have not been established in pediatric patients younger than 1 year of age.

During the conduct of the pediatric studies (STARTS-1 and STARTS-2) *[see Clinical Studies (14)]*, an imbalance in the number of deaths was noted: 5/55 (9.1%), 10/74 (13.5%), and 22/100 (22%) in the sildenafil low, medium, and high dose groups, respectively. The causes of death were related to the progression of PAH. This safety observation in pediatrics was not confirmed in a study conducted in adults designed to evaluate this risk (Study A1481324). Given the beneficial effects on clinical worsening and death observed in adults with increasing doses (Study A1481324) and the expected similarity of disease in pediatrics and adults, a causal association for the observed dose-related effect on mortality in pediatric patients is unlikely, and therefore, the available data support dosing in pediatric patients >45 kg up to a maximum of 40 mg three times a day.

8.5 Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater

frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No dose adjustment is required (including severe impairment CLcr <30 mL/min) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

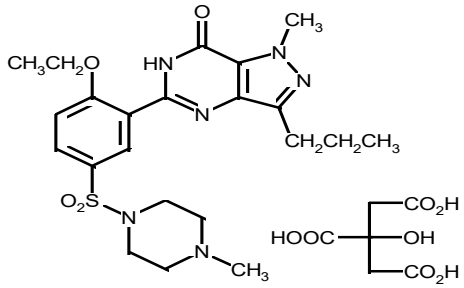
In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

11 DESCRIPTION

REVATIO, phosphodiesterase-5 (PDE-5) inhibitor, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE-5). Sildenafil is also marketed as VIAGRA® for erectile dysfunction.

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7.

REVATIO (sildenafil) Tablets: REVATIO is formulated as white, film-coated round tablets for oral administration. Each tablet contains sildenafil citrate equivalent to 20 mg of sildenafil. In

addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: anhydrous dibasic calcium phosphate, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

REVATIO (sildenafil) Injection: REVATIO is supplied as a clear, colorless, sterile, ready to use solution in a single-use vial containing 10 mg/12.5 mL of sildenafil. Each mL of solution contains 1.124 mg sildenafil citrate (equivalent to 0.8 mg sildenafil), 50.5 mg dextrose, and water for injection.

REVATIO (sildenafil) for Oral Suspension: REVATIO is supplied as white to off-white powders containing 1.57 g of sildenafil citrate (equivalent to1.12 g sildenafil) in an amber glass bottle intended for reconstitution. Following reconstitution with 90 mL water, the total volume of the oral suspension is 112 mL and the oral suspension contains 10 mg/mL sildenafil. The inactive ingredients include citric acid anhydrous, colloidal silicon dioxide anhydrous, grape flavor, sodium benzoate, sodium citrate dihydrate, sorbitol, sucralose, titanium dioxide, and xanthan gum. In addition to the bottle, a press-in bottle adapter and an oral dosing syringe (with 0.5 mL and 2 mL dose markings) are provided.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sildenafil is an inhibitor of cGMP specific PDE-5 in the smooth muscle of the pulmonary vasculature, where PDE-5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with PAH, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, greater than 80-fold for PDE1, greater than 700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE-5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10 times as potent for PDE5 compared to PDE6, an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels *[see Clinical Pharmacology (12.2)]*.

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed *in vitro*, and the mild peripheral arterial-venous dilatation *in vivo*.

12.2 Pharmacodynamics

Effects of REVATIO on Hemodynamic Measures

Adults

Patients on all REVATIO doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo in a study with no background vasodilators *[see SUPER-1 in Clinical Studies (14)]*. Data on other hemodynamic measures for the REVATIO 20 mg three times a day and placebo dosing regimens is displayed in Table 2. The relationship between these effects and improvements in 6-minute walk distance is unknown.

Table 2. Changes from Baseline in Hemodynamic Parameters at Week 12 [mean (95% CI)] for the REVATIO 20 mg Three Times a Day and Placebo Group

	Placebo (n = 65)*	**REVATIO 20 mg (n = 65)***
mPAP (mmHg)	0.6 (-0.8, 2.0)	-2.1 (-4.3, 0.0)
PVR (dyn·s/cm^5)	49 (-54, 153)	-122 (-217, -27)
SVR (dyn·s/cm^5)	-78 (-197, 41)	-167 (-307, -26)
RAP (mmHg)	0.3 (-0.9, 1.5)	-0.8 (-1.9, 0.3)
CO (L/min)	-0.1 (-0.4, 0.2)	0.4 (0.1, 0.7)
HR (beats/min)	-1.3 (-4.1, 1.4)	-3.7 (-5.9, -1.4)

mPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; RAP = right atrial pressure; CO = cardiac output; HR = heart rate.

∗The number of patients per treatment group varied slightly for each parameter due to missing assessments.

Pediatric Patients

Patients on REVATIO medium and high dose groups achieved a dose related improvements in pulmonary vascular resistance index (PVRI) and mean pulmonary arterial pressure (mPAP) compared to those on placebo *[see STARTS-1 in Clinical Studies (14)]*. Improvements were observed with cardiac index in all three REVATIO dose groups over placebo. Data on other hemodynamic measures for the REVATIO low, medium and high dose groups compared to placebo is displayed in Table 3.

Table 3. Placebo Corrected Changes in Hemodynamic Parameters by Dose Group

Parameter [Estimate (95% CI)]	Low Dose	Medium Dose	High Dose
PVRI (%)	-2% (-20%, 20%) n = 37	-18% (-32%, -2%) n = 51	-27% (-39%, -14%) n = 68
mPAP (mmHg)	1.6 (-4.5, 7.6) n = 39	-3.5 (-8.9, 1.9) n = 55	-7.3 (-12.4, -2.1) n = 71
CI (%)	10% (-4%, 26%) n = 37	4% (-7%, 18%) n = 51	15% (3%, 29%) n = 69
SVRI (%)	-9% (-22%, 7%) n = 37	-5% (-17%, 10%) n = 50	-16% (-26%, -4%) n = 68
RAP (mmHg)	-0.17 (-1.91, 1.57) n = 39	-0.19 (-1.73, 1.36) n = 55	-1.14 (-2.61, 0.33) n = 71
HR (%)	3% (-5%, 12%) n = 39	2% (-5%, 9%) n = 55	-2% (-9%, 5%) n = 71

Abbreviations: CI = cardiac index; HR = heart rate; mPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SVRI = systemic vascular resistance index.
Note: n = 52, 56, 55, 54, 56, and 56 placebo patients for PVRI, mPAP, CI, SVRI, RAP and HR, respectively.

Effects of REVATIO on Blood Pressure

Single oral doses of sildenafil 100 mg administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8/5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing and was not different from placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg, and 100 mg doses of sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates *[see Contraindications (4)]*.

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on electrocardiogram (ECG). After chronic dosing of 80 mg three times a day to patients with PAH, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg three times a day sildenafil to healthy volunteers, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 mmHg and 8.4 mmHg, respectively.

After chronic dosing of 80 mg three times a day sildenafil to patients with systemic hypertension, the mean change from baseline in systolic and diastolic blood pressures was a decrease of 9.4 and 9.1 mmHg, respectively.

After chronic dosing of 80 mg three times a day sildenafil to patients with PAH, lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease in both of 2 mmHg).

Effects of REVATIO on Vision

At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to 200 mg revealed no effects of REVATIO on visual acuity, intraocular pressure, or pupillometry.

12.3 Pharmacokinetics

Absorption and Distribution

REVATIO is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25 to 63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When REVATIO is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Bioequivalence was established between the 20 mg tablet and the 10 mg/mL oral suspension when administered as a 20 mg single oral dose of sildenafil (as citrate).

Metabolism and Excretion

Sildenafil is cleared predominantly by the CYP3A (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE-5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with PAH, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours.

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

REVATIO Injection: The pharmacokinetic profile of REVATIO has been characterized following intravenous administration. A 10 mg dose of REVATIO Injection is predicted to provide a pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

Population Pharmacokinetics

Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in patients with PAH. The dataset available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a significant impact on sildenafil pharmacokinetics in patients with PAH.

In patients with PAH, the average steady-state concentrations were 20 to 50% higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with PAH compared to healthy volunteers.

Pediatric Patients

Body weight was shown to be a good predictor of drug exposure in children. Sildenafil plasma concentration half-life values were estimated to range from 2.9 to 4.4 hours for a range of 10 to 70 kg of body weight. T_{max} was estimated at approximately 1 hour.

Geriatric Patients

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 84% and 107% higher plasma concentrations of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy younger volunteers (18 to 45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.

Renal Impairment

In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CLcr less than 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 200% and 79%, respectively, in patients with severe renal impairment compared to patients with normal renal function.

Hepatic Impairment

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh class A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

Drug Interaction Studies

In vitro studies

Sildenafil metabolism is principally mediated by the CYP3A (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

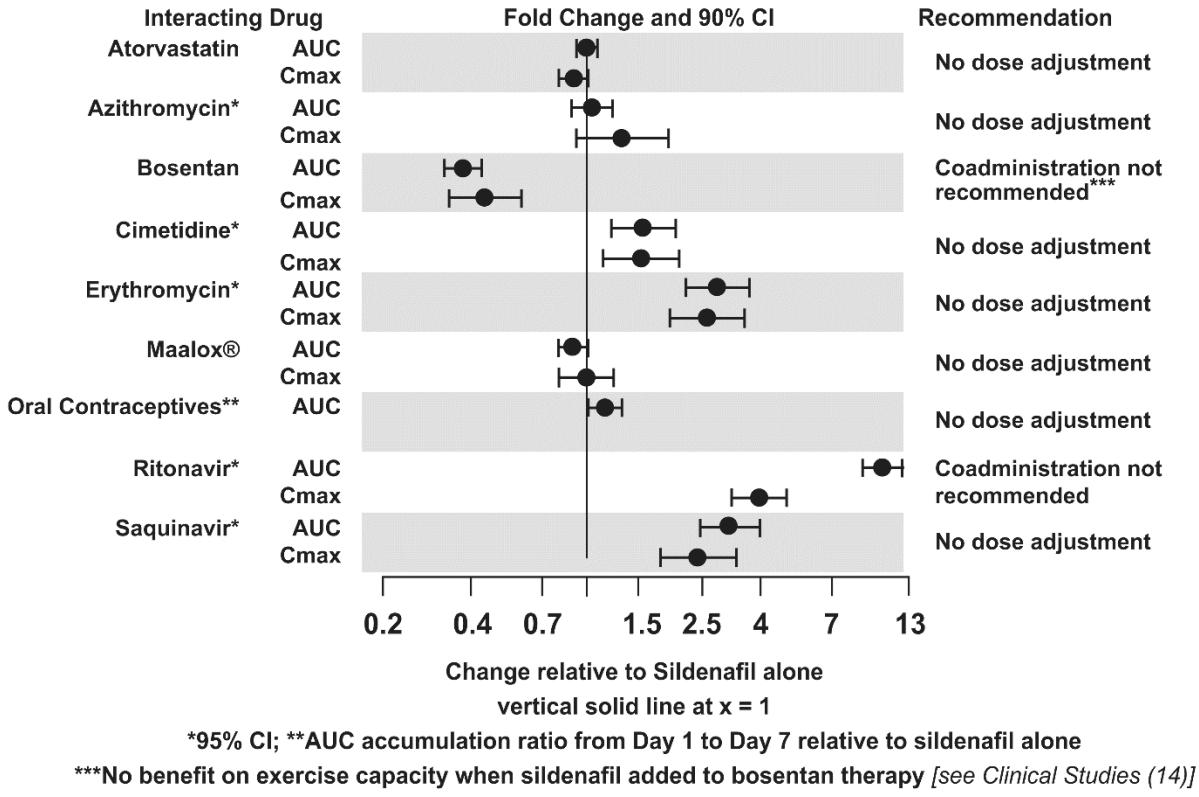
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A (IC50 greater than150 μM).

Sildenafil is not expected to affect the pharmacokinetics of compounds which are substrates of these CYP enzymes at clinically relevant concentrations.

In vivo studies

The effects of other drugs on sildenafil pharmacokinetics and the effects of sildenafil on the exposure to other drugs are shown in Figure 1 and Figure 2, respectively.

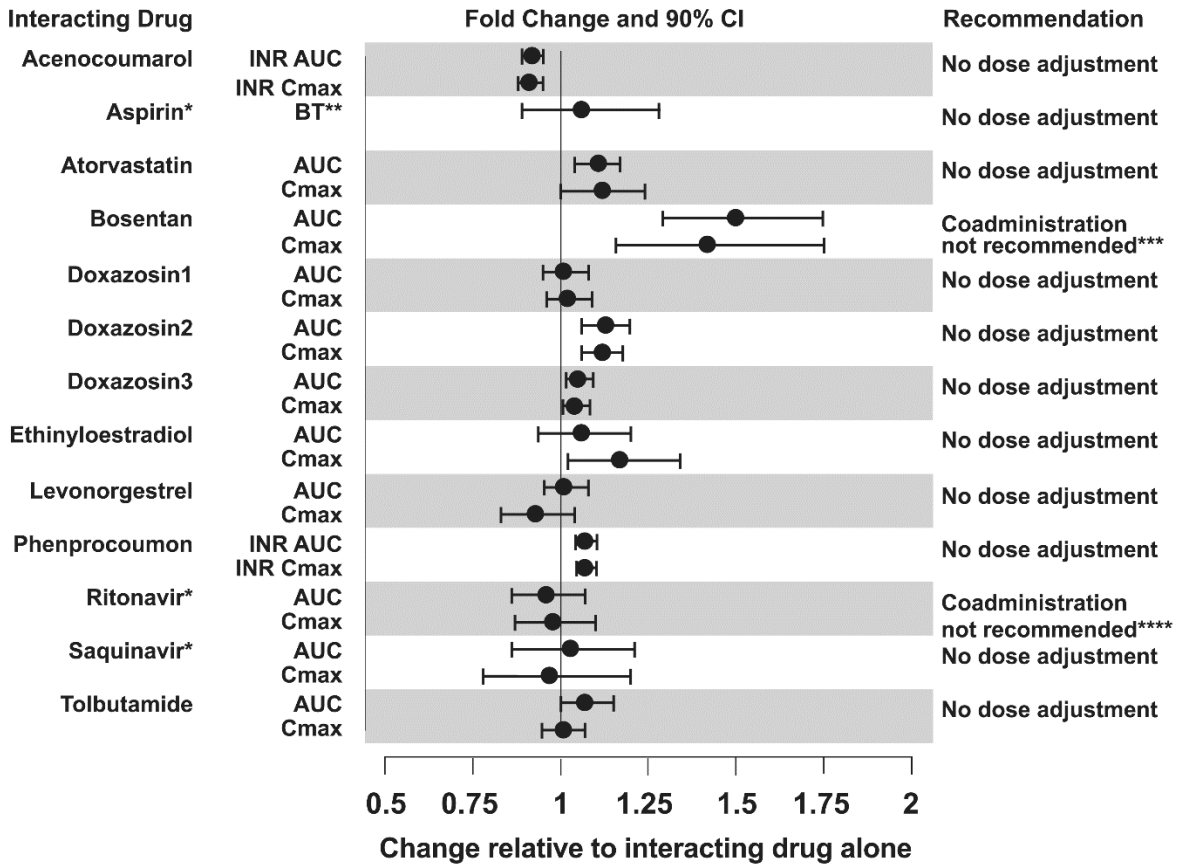
Figure 1. Effects of Other Drugs on Sildenafil Pharmacokinetics



*95% CI; **AUC accumulation ratio from Day 1 to Day 7 relative to sildenafil alone

***No benefit on exercise capacity when sildenafil added to bosentan therapy *[see Clinical Studies (14)]*

Figure 2. Effects of Sildenafil on Other Drugs



vertical solid line at x = 1

Doxazosin1, 25 mg; 2, 50 mg; and 3, 100 mg sildenafil; *95% CI; **BT = bleeding time

***No benefit on exercise capacity when sildenafil added to bosentan therapy *[see Clinical Studies (14)]*

****based on the effect of ritonavir on sildenafil PK

CYP3A Inhibitors and Beta Blockers

Population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 30% reduction in sildenafil clearance when it was co-administered with mild/moderate CYP3A inhibitors and an approximately 34% reductions in sildenafil clearance when co-administered with beta-blockers. Sildenafil exposure at a dose of 80 mg three times a day without concomitant medication is shown to be 5-fold the exposure at a dose of 20 mg three times a day. This concentration range covers the same increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir).

REVATIO Injection: Predictions based on a pharmacokinetic model suggest that drug-drug interactions with CYP3A inhibitors will be less than those observed after oral sildenafil administration.

CYP3A4 Inducers Including Bosentan

Concomitant administration of strong CYP3A inducers is expected to cause substantial decreases in plasma levels of sildenafil.

Population pharmacokinetic analysis of data from patients in clinical trials indicated approximately 3-fold the sildenafil clearance when it was co-administered with mild CYP3A inducers.

Epoprostenol

The mean reduction of sildenafil (80 mg three times a day) bioavailability when co-administered with epoprostenol was 28%, resulting in about 22% lower mean average steady state concentrations. Therefore, the slight decrease of sildenafil exposure in the presence of epoprostenol is not considered clinically relevant. The effect of sildenafil on epoprostenol pharmacokinetics is not known.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Alcohol

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33- and 37-times, for male and female rats, respectively, the human exposure at the RHD of 20 mg three times a day. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19- and 38-times for males and females, respectively, the human exposure at the RHD of 20 mg three times a day.

14 CLINICAL STUDIES

SUPER-1 (NCT00644605) - REVATIO monotherapy [20 mg, 40 mg, and 80 mg three times a day]

A randomized, double-blind, placebo-controlled study of REVATIO (SUPER-1) was conducted in 277 patients with PAH (defined as a mean pulmonary artery pressure ≥25 mmHg at rest with a pulmonary capillary wedge pressure <15 mmHg). Patients were predominantly WHO Functional Classes II-III. Allowed background therapy included a combination of anticoagulants, digoxin, calcium channel blockers, diuretics, and oxygen. The use of prostacyclin analogues, endothelin receptor antagonists, and arginine supplementation were not permitted. Patients who had failed to respond to bosentan were also excluded. Patients with left ventricular ejection fraction less than 45% or left ventricular shortening fraction less than 0.2 also were not studied.

Patients were randomized to receive placebo (n = 70) or REVATIO 20 mg (n = 69), 40 mg (n = 67) or 80 mg (n = 71) three times a day for a period of 12 weeks. They had either primary pulmonary hypertension (PPH) (63%), PAH associated with CTD (30%), or PAH following surgical repair of left-to-right congenital heart lesions (7%). The study population consisted of 25% men and 75% women with a mean age of 49 years (range: 18 to 81 years) and baseline 6-minute walk distance between 100 and 450 meters (mean 343).

The primary efficacy endpoint was the change from baseline at Week 12 (at least 4 hours after the last dose) in the 6-minute walk distance. Placebo-corrected mean increases in walk distance of 45-50 meters were observed with all doses of REVATIO. These increases were significantly different from placebo, but the REVATIO dose groups were not different from each other (see Figure 3), indicating no additional clinical benefit from doses higher than 20 mg three times a day. The improvement in walk distance was apparent after 4 weeks of treatment and was maintained at Week 8 and Week 12.

Figure 3. Change from Baseline in 6-Minute Walk Distance (meters) at Weeks 4, 8, and 12 in SUPER-1: Mean (95% Confidence Interval)

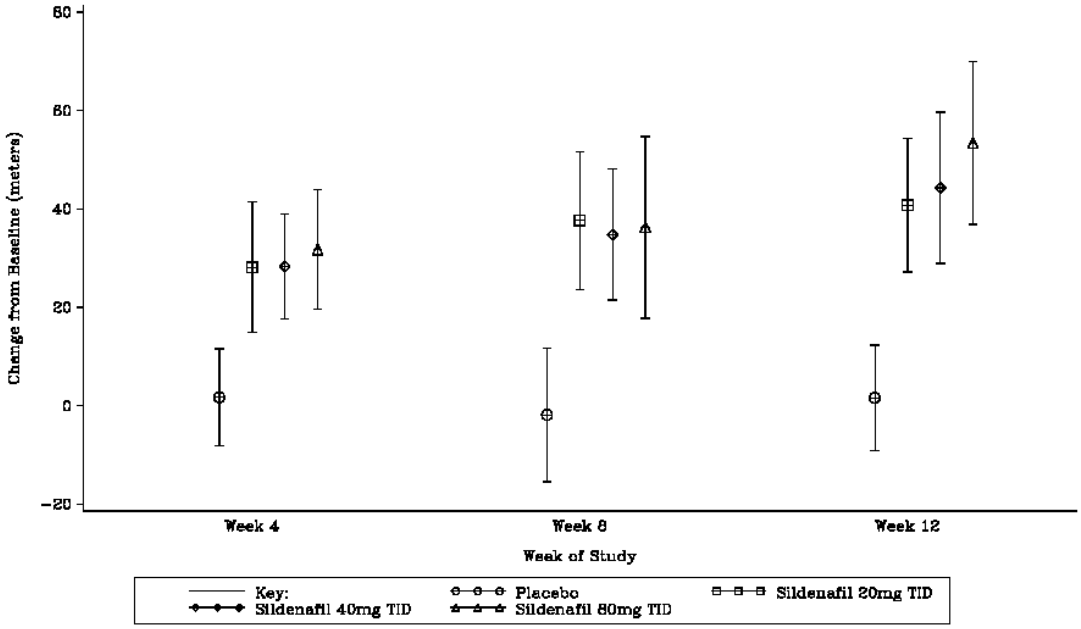
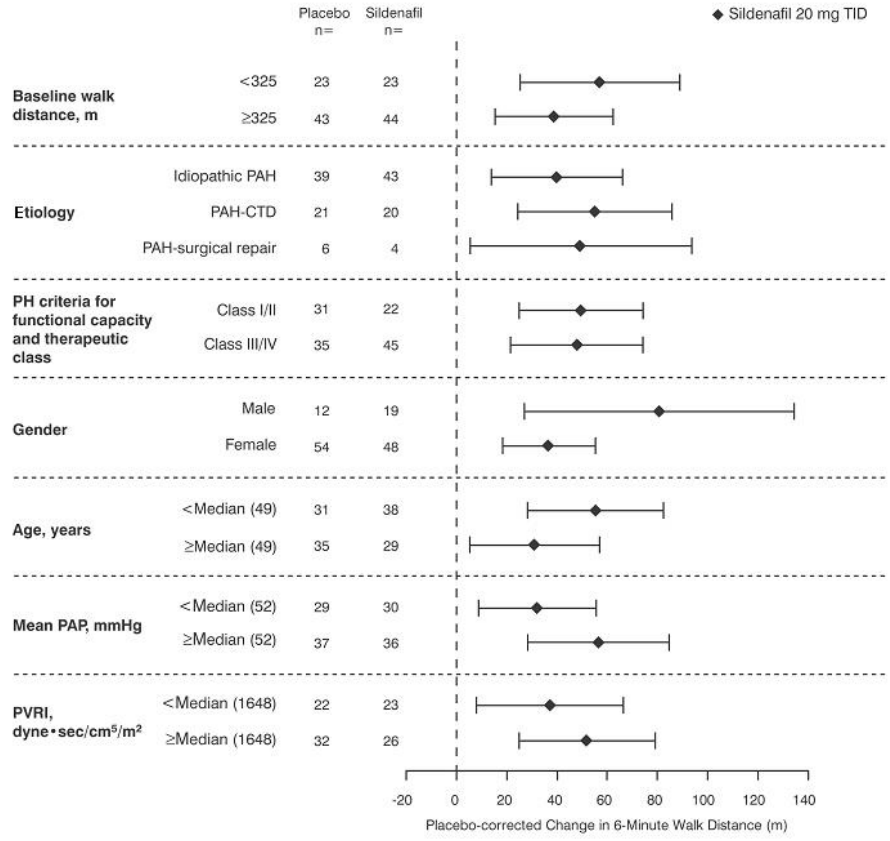


Figure 4 displays subgroup efficacy analyses in SUPER-1 for the change from baseline in 6-Minute Walk Distance at Week 12 including baseline walk distance, disease etiology, functional class, gender, age, and hemodynamic parameters.

Figure 4. Placebo-Corrected Change From Baseline in 6-Minute Walk Distance (meters) at Week 12 by Study Subpopulation in SUPER-1: Mean (95% Confidence Interval)



Key: PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PH = pulmonary hypertension; PAP = pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; TID = three times daily.

SUPER-2 (NCT00159887) Long-term Treatment of PAH

In a long-term follow-up of patients who were treated with sildenafil (n=277), K-M estimates of survival at 1, 2, and 3 years were 94%, 88% , and 79%, respectively. These uncontrolled observations do not allow comparison with a group not given sildenafil and cannot be used to determine the long term-effect of sildenafil on mortality.

PACES-1 (NCT00159861) - REVATIO Co-administered with Epoprostenol

A randomized, double-blind, placebo-controlled study (PACES-1) was conducted in 267 patients with PAH who were taking stable doses of intravenous epoprostenol. Patients had to have a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg and a pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg at rest via right heart catheterization within 21 days before randomization, and a baseline 6-minute walk test distance greater than or equal to 100 meters and less than or equal to 450 meters (mean 349 meters). Patients were randomized to placebo or REVATIO (in a fixed titration starting from 20 mg to 40

mg and then 80 mg, three times a day) and all patients continued intravenous epoprostenol therapy.

At baseline patients had PPH (80%) or PAH secondary to CTD (20%); WHO Functional Class I (1%), II (26%), III (67%), or IV (6%); and the mean age was 48 years, 80% were female, and 79% were Caucasian.

There was a statistically significant greater increase from baseline in 6-minute walk distance at Week 16 (primary endpoint) for the REVATIO group compared with the placebo group. The mean change from baseline at Week 16 (last observation carried forward) was 30 meters for the REVATIO group compared with 4 meters for the placebo group giving an adjusted treatment difference of 26 meters (95% CI: 10.8, 41.2) (p = 0.0009).

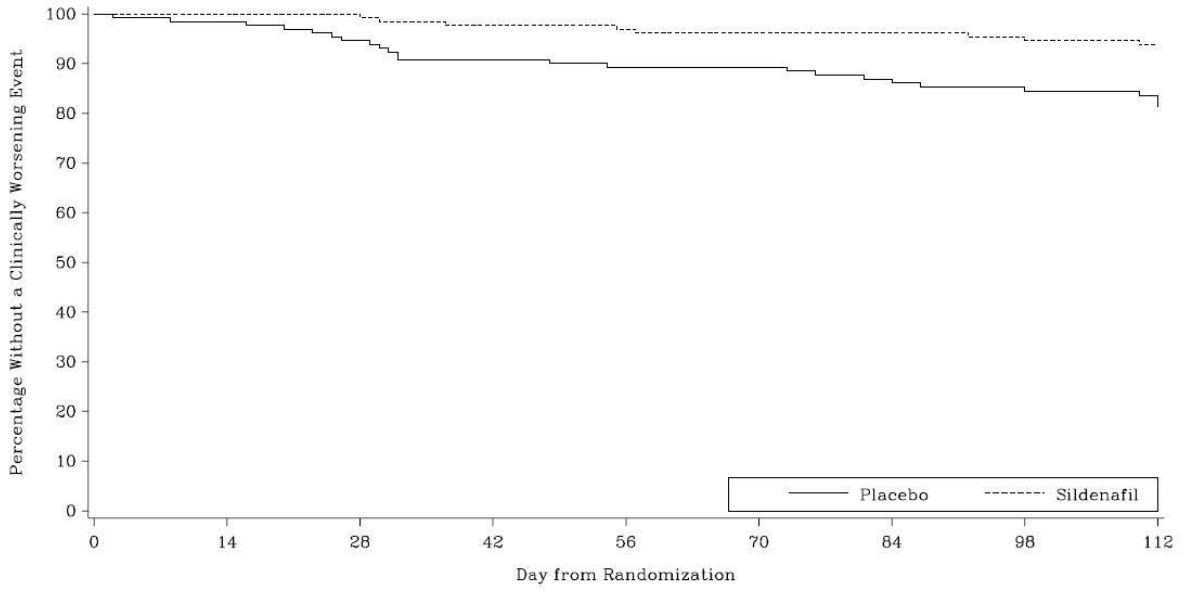
Patients on REVATIO achieved a statistically significant reduction in mPAP compared to those on placebo. A mean placebo-corrected treatment effect of -3.9 mmHg was observed in favor of REVATIO (95% CI: -5.7, -2.1) (p = 0.00003).

Time to clinical worsening of PAH was defined as the time from randomization to the first occurrence of a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy). Table 4 displays the number of patients with clinical worsening events in PACES-1. Kaplan-Meier estimates and a stratified log-rank test demonstrated that placebo-treated patients were 3 times more likely to experience a clinical worsening event than REVATIO-treated patients and that REVATIO-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0074). Kaplan-Meier plot of time to clinical worsening is presented in Figure 5.

Table 4. Clinical Worsening Events in PACES-1

	Placebo (N = 131)		**REVATIO (N = 134)**	
Number of patients with clinical worsening first event	23		8	
	First Event	**All Events**	**First Event**	**All Events**
Death, n	3	4	0	0
Lung transplantation, n	1	1	0	0
Hospitalization due to PAH, n	9	11	8	8
Clinical deterioration resulting in:				
Change of Epoprostenol Dose, n	9	16	0	2
Initiation of Bosentan, n	1	1	0	0
Proportion worsened	0.187		0.062	
95% Confidence Interval	(0.12 – 0.26)		(0.02 – 0.10)	

Figure 5. Kaplan-Meier Plot of Time (in Days) to Clinical Worsening of PAH in PACES-1



Improvements in WHO Functional Class for PAH were also demonstrated in patients on REVATIO compared to placebo. More than twice as many REVATIO-treated patients (36%) as placebo-treated patients (14%) showed an improvement in at least one functional New York Heart Association (NYHA) class for PAH.

Study A1481243 (NCT00323297) - REVATIO Added to Bosentan Therapy – Lack of Effect on Exercise Capacity

A randomized, double-blind, placebo-controlled study was conducted in 103 patients with PAH who were on bosentan therapy for a minimum of 3 months. The PAH patients included those with primary PAH and PAH associated with CTD. Patients were randomized to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62.5 to 125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6-minute walk distance (6MWD). The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil 20 mg plus bosentan and bosentan alone.

STARTS-1 (NCT00159913) - Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension

A total of 234 patients with PAH aged 1 to 17 years were treated in a randomized, double-blind, multi-center, placebo-controlled parallel group, dose-ranging study. Patients (38% male and 62% female) had body weight ≥8 kg and had idiopathic pulmonary arterial hypertension (33%), or PAH associated with congenital heart disease (systemic-to-pulmonary shunt 37%, surgical repair 30%). In this trial, 27% of patients were <7 years old. Patients were WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%).

Patients were naïve for specific PAH therapy and the use of prostacyclin, prostacyclin analogues and endothelin receptor antagonists were not permitted in the study, and neither were arginine supplementation, nitrates, alpha-blockers and potent CYP450 3A4 inhibitors.

The primary objective of the study was to assess the effect of REVATIO on percent change from baseline in PVO_2, normalized to body weight, from baseline to week 16 as measured by the Cardiopulmonary Exercise Test (CPET) (patients who were developmentally able to perform the test, n = 115). Secondary endpoints included hemodynamic monitoring, symptom assessment, WHO Functional Class, change in background treatment, and quality of life measurements (n = 234).

Patients were allocated to one of three sildenafil treatment groups (low, medium, or high) or placebo. Actual doses administered were dependent on body weight (see Table 5).

Table 5. Treatment Allocation by Dose and Body Weight in Pediatric Study

	Placebo	**Low Dose**		**Medium Dose**		**High Dose**	
Body Weight (kg)	**N**	**Dose**	**N**	**Dose**	**N**	**Dose**	**N**
≥8 - 20	18		na	10 mg	15	20 mg	35
>20 - 45	32	10 mg	31	20 mg	30	40 mg	31
>45	10	10 mg	11	40 mg	10	80 mg	11

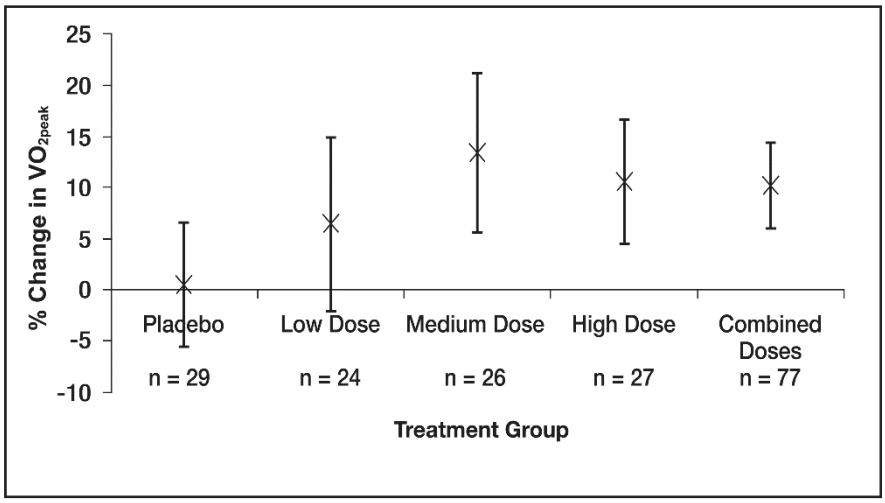
The proportion of patients receiving supportive medicinal products at baseline (anticoagulants, digoxin, calcium channel blockers, diuretics and/or oxygen) was similar in the combined sildenafil treatment group (48%) and the placebo treatment group (42%).

The primary endpoint was a percentage change in VO_{2peak} from baseline to week 16 assessed by CPET. Mean baseline peak volume of oxygen consumed (VO_2) values were similar across the sildenafil treatment groups (17 to 18 ml/kg/min), and slightly higher for the placebo treatment group (20 ml/kg/min). See Figure 6.

A total of 45% of patients were evaluable for CPET, which comprised those children ≥7 years old and developmentally able to perform the test. Children <7 years were evaluable only for the secondary endpoints.

Mean increases in VO_{2peak} percentage change from baseline at Week 16, were observed with all 3 sildenafil doses (range of 6% to 13%, Figure 6), with little change with placebo (0.5%).

Figure 6. Percentage Change from Baseline in VO2Peak: Mean (95% Confidence Intervals)



The estimated difference between the combined sildenafil doses and placebo was 8% (95% CI: -0.2 to 16). The results of the main analysis (combined dose groups versus placebo) were not statistically significant (p=0.056).

The estimated difference between the sildenafil medium dose group and placebo was 11±5% (95% CI: 2 to 21).

Impact on Hemodynamic Parameters
Dose related improvements were observed with PVRI and mPAP. Statistically significant PVRI reductions compared to placebo were seen with the sildenafil medium and high dose groups (18% [95% CI: -32% to -2%] and 27% [95% CI: -39% to -14%], respectively) but not the low dose group (2% (95% CI: -20%, 20%). The sildenafil medium and high dose groups displayed mPAP changes from baseline compared to placebo, of -3.5 mmHg (95% CI: -8.9, 1.9) and -7.3 mmHg (95% CI: -12.4, -2.1), respectively; while the low dose group showed little difference from placebo (difference of 1.6 mmHg [95% CI: -4.5, 7.6]). Improvements were observed with cardiac index with all three sildenafil groups over placebo, 10%, 4%, and 15% for the low, medium, and high dose groups, respectively *[see Clinical Pharmacology (12.2)]*.

STARTS-2 (NCT00159874) - Long-Term Survival with Oral Sildenafil Monotherapy in Treatment-Naïve Pediatric Pulmonary Arterial Hypertension

Of the 234 pediatric patients treated in the short-term, placebo-controlled study, 220 patients entered the long-term extension study. Patients who had been in the placebo group in the short-term study were randomly reassigned to sildenafil treatment; patients weighing ≤20 kg entered the medium or high dose groups (1:2), while patients weighing >20 kg entered the low, medium, or high dose groups (1:1:1). Of the total 229 patients who received sildenafil, there were 55, 74, and 100 patients in the low, medium, and high dose groups, respectively. Across the short-term and long-term studies, the overall duration of treatment from start of double-blind for individual patients ranged from 3 to 3,129 days. By sildenafil treatment group, median duration of sildenafil

treatment was 1,696 days (excluding the 5 patients who received placebo in double-blind and were not treated in the long-term extension study).

Peak VO_2 was assessed 1 year after the start of the placebo-controlled study. Of sildenafil-treated patients developmentally able to perform the CPET 59/114 patients (52%) had not shown any deterioration in PVO_2 from start of sildenafil. Similarly, 191 of 229 patients (83%) who had received sildenafil had either maintained or improved their WHO Functional Class at 1 year assessment.

Kaplan-Meier estimates of survival at 3 years in patients >20 kg in weight at baseline were 94%, 93%, and 85% in the low, medium, and high dose groups, respectively; for patients ≤20 kg in weight at baseline, the survival estimates were 94% and 93% for patients in the medium and high dose groups, respectively *[see Use in Specific Populations (8.4) and Adverse Reactions (6.1)]*.

Study A1481324 (NCT02060487) - Study to Assess the Effects of REVATIO on Mortality in Adults with PAH

A study to assess the effects of multiple doses of sildenafil on mortality in adults with PAH was conducted following the observation of a higher risk of mortality in pediatric patients taking a high dose of REVATIO TID, based on body weight, compared to those taking a lower dose of REVATIO in the long-term extension of the pediatric clinical trial.

The study was a randomized, double-blind, parallel-group study in 385 adults with PAH. Patients were randomly assigned 1:1:1 to one of three treatment groups (5, 20, and 80 mg TID). Most patients were PAH treatment naïve (83%). For most patients the etiology of PAH was idiopathic (72%). The most common WHO Functional Class was Class III (58% of patients). Treatment groups were well balanced with respect to baseline demographics of strata history of PAH treatment and etiology of PAH, as well as the WHO Functional Class categories.

The primary objective of the study was to compare sildenafil 80 mg TID versus 5 mg TID for mortality, with success defined by ruling out twice the mortality at 80 mg.

The key secondary efficacy endpoint was time to first event of clinical worsening, defined as a composite endpoint of all-cause mortality, hospitalization for worsening PAH or disease progression. An additional secondary endpoint was 6MWD at Months 6 and 12.

Overall Survival
At the time of a planned interim analysis (50% deaths) it was identified that the primary efficacy objective of this protocol was met and therefore the study was stopped. Based on the primary efficacy endpoint (mortality), the non-inferiority of sildenafil 80 mg TID arm versus 5 mg TID arm was met using a 2-sided significance level of 0.003 for the interim analysis. Primary comparison of the 80 mg TID group to the 5-mg TID group yielded the HR (99.7% CI) = 0.51 (0.22, 1.21); i.e., non-inferiority was established.

Table 6. Hazard Ratios for Overall Survival, Assessed in the Proportional Hazards Model – Intent To Treat Population

	Sildenafil 5 mg N = 129	Sildenafil 20 mg N = 128	Sildenafil 80 mg N = 128
Patient-years of follow-up	329.8	340.5	356.7
Number of deaths (%)	34 (26)	25 (20)	19 (15)
On treatment deaths[a] (%)	22 (17)	13 (10)	15 (12)
Off treatment deaths (%)	12 (9)	12 (9)	4 (3)
Hazard ratio relative to sildenafil 5 mg			
Hazard ratio estimate[b]		0.68	0.51
99.7% CI		0.31, 1.49	0.22, 1.21
Hazard ratio relative to sildenafil 20 mg			
Hazard ratio estimate			0.74
99.7% CI			0.30 1.84

a. On treatment deaths: Any death within 7 days of last dose was regarded as "On treatment", thus might include deaths occurred after discontinuation from study treatment

b. Hazard ratio estimates from the proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Kaplan-Meier estimates of survival at 3 years were 66%, 79%, and 85% in the 5-, 20-, and 80-mg TID dose groups, respectively

Clinical Worsening

Sildenafil 80 mg was also superior to 5 mg for time to first event of clinical worsening with HR (99.7% CI) = 0.44 (0.22, 0.89).

Table 7. Hazard Ratios for Time to First Event of Clinical Worsening – Intent To Treat Population

	Sildenafil 5 mg N = 129	Sildenafil 20 mg N = 128	Sildenafil 80 mg N = 128
Patient-years of follow-up	249.6	276.4	306.5
Number of patients with clinical worsening	52	36	28
First Event of clinical worsening[a] n (%)			
Disease progression[b]	8 (6)	2 (2)	6 (5)
Hospitalization for PAH[c]	28 (22)	23 (18)	11 (9)
Death[d]	16 (12)	11 (9)	11 (9)
Hazard ratio relative to sildenafil 5 mg			
Hazard ratio estimate[e]		0.63	0.44
99.7% CI		0.33, 1.21	0.22, 0.89
p-value		0.035	<0.001
Hazard ratio relative to sildenafil 20 mg			
Hazard ratio estimate[e]			0.72
99.7% CI			0.34, 1.52
p-value			0.195

Note: Sildenafil 5 mg is not an approved dosage.

Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; PAH = pulmonary arterial hypertension.

a. Clinical worsening events were defined as reduction from baseline in the 6MWD test by at least 15% and worsening functional class from baseline, both confirmed by a second test/evaluation within 2 weeks.
b. Count of cases of disease progression as the first event of clinical worsening.
c. Count of non-elective hospital stays for worsening PAH as the first event of clinical worsening.
d. Count of deaths as the first event of clinical worsening.
e. Hazard ratio estimates from the proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH. P-value from the Wald test.

6MWD at Months 6 and 12

At baseline, the median of 6MWD for the intent-to-treat (ITT) population was 332 to 352 m. At Month 6, the median change from baseline was highest for sildenafil 80 mg TID with 28 m compared to 18 m and 19 m for sildenafil 5 mg TID and sildenafil 20 mg TID groups, respectively. The same was seen at Month 12, the median change from baseline for sildenafil 80 mg TID group was 33 m compared to 17 m for sildenafil 5 mg TID and 31 m in sildenafil 20 mg TID groups.

Overall, the safety data for sildenafil 20 mg TID and for the higher sildenafil 80 mg TID dose were consistent with the established safety profile of sildenafil in previous adult PAH studies *[see Adverse Reactions (6.1)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

REVATIO tablets are supplied as white, film-coated, round tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

REVATIO Tablets			
Package Configuration	Strength	NDC	Engraving on Tablet
Bottle of 90 Tablets	20 mg	0069-4190-68	RVT20

Recommended Storage for REVATIO Tablets: Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

REVATIO injection is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg sildenafil/12.5 mL presented in a single-use glass vial.

REVATIO Injection		
Package Configuration	Strength	NDC
Vial individually packaged in a carton	10 mg /12.5 mL	0069-0338-01

Recommended Storage for REVATIO Injection: Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

REVATIO powder for oral suspension is supplied in amber glass bottles. Each bottle contains white to off-white powders containing 1.57 g of sildenafil citrate (equivalent to 1.12 g sildenafil). Following reconstitution, the total volume of the oral suspension is 112 mL (10 mg sildenafil/mL). A 2 mL oral dosing syringe (with 0.5 mL and 2 mL dose markings) and a press-in bottle adaptor are also provided.

REVATIO Powder for Oral Suspension		
Package Configuration	Strength	NDC
Powder for oral suspension - bottle	10 mg/mL (when reconstituted)	0069-0336-21

Recommended storage for REVATIO for oral suspension: Store below 30°C (86°F) in the original package in order to protect from moisture.

Recommended storage for reconstituted oral suspension: Store below 30°C (86°F) or in refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. The shelf-life of the reconstituted oral

suspension is 60 days. Any remaining oral suspension should be discarded 60 days after reconstitution.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

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UPJ:RVTTOSI:RX2

PATIENT INFORMATION

REVATIO® (re-VAH-tee-oh)
(sildenafil)
tablets

REVATIO® (re-VAH-tee-oh)
(sildenafil)
oral suspension

What is the most important information I should know about REVATIO?
Never take REVATIO with any nitrate or guanylate cyclase stimulator medicines.

- Your blood pressure could drop quickly to an unsafe level.

Nitrates include:

- Medicines that treat chest pain (angina)
- Nitroglycerin in any form including tablets, patches, sprays, and ointments
- Isosorbide mononitrate or dinitrate
- Street drugs called "poppers" (amyl nitrate, butyl nitrate or nitrite)

Guanylate cyclase stimulators include:

- Riociguat, a medicine that treats pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

Ask your healthcare provider or pharmacist if you are not sure if you or your child are taking a nitrate or a guanylate cyclase stimulator medicine.
See **"What are the possible side effects of REVATIO?"** for more information about side effects.

What is REVATIO?
REVATIO is a prescription medicine used to treat pulmonary arterial hypertension (PAH). PAH is a type of high blood pressure in the arteries of your lungs. REVATIO may be used in:

- adults to improve your ability to exercise and help slow down the worsening of your physical condition.
- children 1 to 17 years old to improve their ability to exercise, and in children too young to do certain exercise and lung testing.

It is not known if REVATIO is safe and effective in children younger than 1 year of age.

Do not take REVATIO if you or your child:

- take medicines called nitrates.
- take riociguat, a guanylate cyclase stimulator medicine.
- are allergic to sildenafil or any of the ingredients in REVATIO. See the end of this leaflet for a complete list of ingredients in REVATIO.

Before taking REVATIO, tell your healthcare provider about all of your medical conditions, including if you or your child:

- have low blood pressure
- have heart problems
- have pulmonary veno-occlusive disease (PVOD)
- have bleeding problems or a stomach (peptic) ulcer. It is not known if REVATIO is safe in people with bleeding problems or who have a stomach ulcer.
- have an eye problem called retinitis pigmentosa
- have ever had sudden loss of vision in one or both eyes, including an eye problem called non-arteritic anterior ischemic optic neuropathy (NAION)
- have ever had hearing problems such as ringing in the ears, dizziness, or loss of hearing
- have a deformed penis shape or Peyronie's disease
- have any blood cell problems such as sickle cell anemia
- are pregnant or plan to become pregnant. It is not known if REVATIO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. REVATIO passes into your breast milk. It is not known if it can harm your baby. Talk with your healthcare provider about the best way to feed your baby during treatment with REVATIO.

Tell your healthcare provider about all of the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. REVATIO and certain other medicines may affect each other and can cause side effects.

Especially tell your healthcare provider if you or your child take:

- nitrates or guanylate cyclase stimulators. See "**What is the most important information I should know about**

REVATIO?"

- medicines to treat high blood pressure
- medicines for erectile dysfunction (impotence). REVATIO contains sildenafil, which is the same medicine found in another medicine called VIAGRA®. VIAGRA is used for the treatment of erectile dysfunction. **Do not** take VIAGRA or other PDE-5 inhibitors during treatment with REVATIO.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you or your child take. Keep a list of your or your child's medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take REVATIO?

- Take or give REVATIO exactly as your healthcare provider tells you.
- Your healthcare provider may change your or your child's dose of REVATIO as needed. Do not change your dose or stop taking REVATIO without talking to your healthcare provider.
- REVATIO may be prescribed to you as REVATIO tablets or REVATIO oral suspension.
- Take your prescribed dose of REVATIO tablets or oral suspension 3 times a day.
- **See the detailed Instructions for Use that comes with REVATIO oral suspension for information on how to take or give REVATIO oral suspension.** REVATIO oral suspension will be mixed for you by your pharmacist. Do not mix REVATIO oral suspension with other medicine or flavoring.
- If you or your child take too much REVATIO, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of REVATIO?

REVATIO may cause serious side effects, including:

- See **"What is the most important information I should know about REVATIO?"**
- **Decreased blood pressure.** REVATIO may cause low blood pressure that last for a short time. If you take medicines to treat high blood pressure, your healthcare provider should monitor your blood pressure during treatment with REVATIO.
- **Decreased eyesight or permanent loss of vision in one or both eyes** can be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). Most people who develop NAION have certain risk factors. You can ask your healthcare provider if you have questions about risk factors for NAION. If you notice a sudden decrease or loss of vision in one or both eyes during treatment with REVATIO, contact your healthcare provider right away.
- **Sudden decrease or loss of hearing**, sometimes with ringing in the ears and dizziness**.** If you notice a sudden decrease or loss of hearing during treatment with REVATIO, contact your healthcare provider right away.
- **In men, an erection that lasts for more than 4 hours (priapism).** If you have an erection, with or without pain, that lasts more than 4 hours, contact your healthcare provider or get emergency medical help right away. A painful erection that lasts more than 6 hours must be treated right away or you can have lasting damage to your penis, including the inability to have erections.

The most common side effects of REVATIO in adults include:

- nosebleeds
- headache
- upset stomach
- getting red or hot in the face (flushing)
- arm or leg pain
- muscle aches and pain
- back pain
- diarrhea

The most common side effect of REVATIO in children is an erection that lasts for more than 4 hours (priapism).

These are not all the possible side effects of REVATIO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store REVATIO?

- Store REVATIO tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store mixed (reconstituted) REVATIO oral suspension below 86°F (30°C) or in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze mixed REVATIO oral suspension.
- Throw away (discard) any remaining REVATIO oral suspension 60 days after mixed by the pharmacist. See the "Discard after" date written on the bottle label.

Keep REVATIO and all medicines out of the reach of children.

General information about the safe and effective use of REVATIO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use REVATIO for a condition for which it was not prescribed. Do not give REVATIO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about REVATIO that is written for health professionals.

What are the ingredients in REVATIO?

Active ingredients: sildenafil citrate

Inactive ingredients:

REVATIO tablets: anhydrous dibasic calcium phosphate, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin

REVATIO oral suspension: citric acid anhydrous, colloidal silicon dioxide anhydrous, grape flavor, sodium benzoate, sodium citrate dihydrate, sorbitol, sucralose, titanium dioxide, and xanthan gum

Distributed by:
Viatris Specialty LLC
Morgantown, WV 26505 U.S.A.

UPJ:PL:RVTTOSI:RX2
For more information call Viatris at 1-877-446-3679 (1-877-4-INFO-RX).

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: January 2023

Instructions for Use
REVATIO® (re-VAH-tee-oh)
(sildenafil)
oral suspension

Read this Instructions for Use before you start taking REVATIO oral suspension or giving REVATIO oral suspension to your child and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your or your child's medical condition or treatment.

Important information:

- Ask your healthcare provider or pharmacist to show you how to measure and take or give your child's prescribed dose of REVATIO oral suspension.
- Your pharmacist will mix (reconstitute) REVATIO oral suspension before it is given to you. **Do not** take or give REVATIO oral suspension and contact your pharmacist if the medicine in the bottle is still a powder.
- Always use the oral dosing syringe that comes with REVATIO oral suspension. If your carton does not come with an oral dosing syringe, contact your pharmacist.
- **Do not** take or give REVATIO oral suspension if the bottle adaptor is not in the bottle. If the bottle adaptor is not in the bottle, contact your pharmacist.
- REVATIO oral suspension should not be mixed with any other medicine or flavoring.

Supplies you will need to take or give a dose of REVATIO oral suspension (See Figure A):

- 1 bottle of REVATIO oral suspension with pre-inserted bottle adaptor
- 1 oral dosing syringe (provided in the carton)

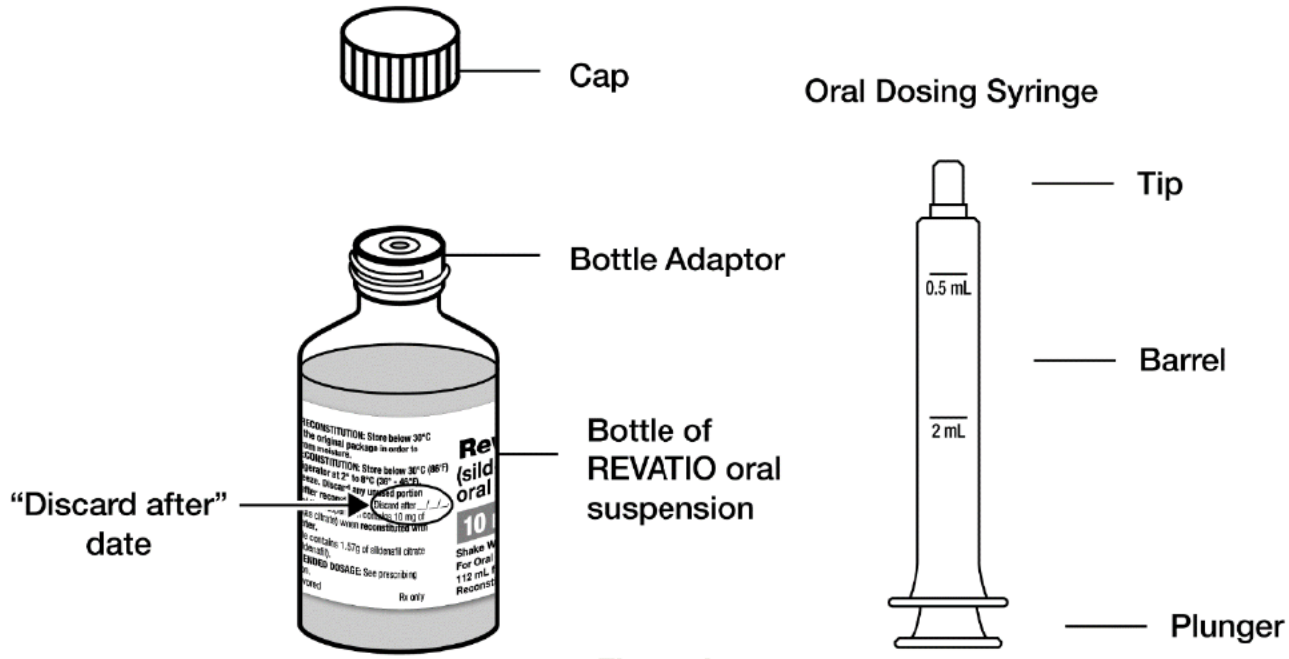

Figure A

Step 1. Shake the bottle of REVATIO oral suspension for 10 seconds before each use. (See Figure B)

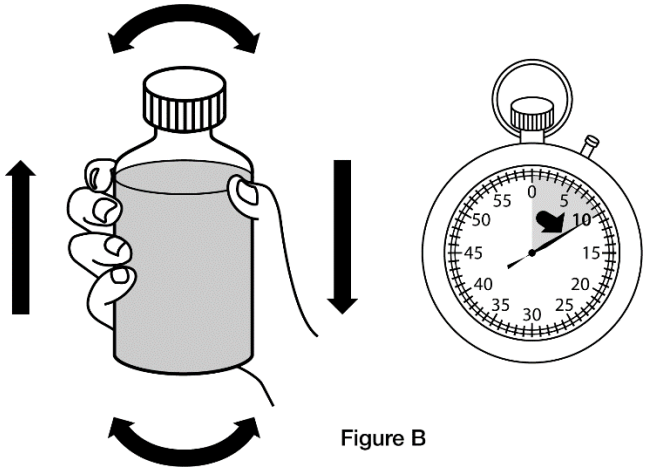

Figure B

Step 2. Remove the cap. Open the bottle by pushing down on the cap and twisting it in the direction of the arrow (counter-clockwise). (See Figure C)

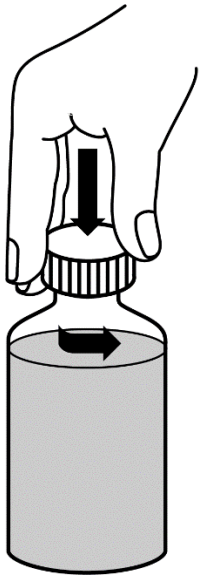

Figure C

Step 3. Fully push down (depress) the plunger of the oral dosing syringe. Then insert the tip of the oral dosing syringe into the bottle adaptor while holding the bottle upright, on a flat surface. (See Figure D)

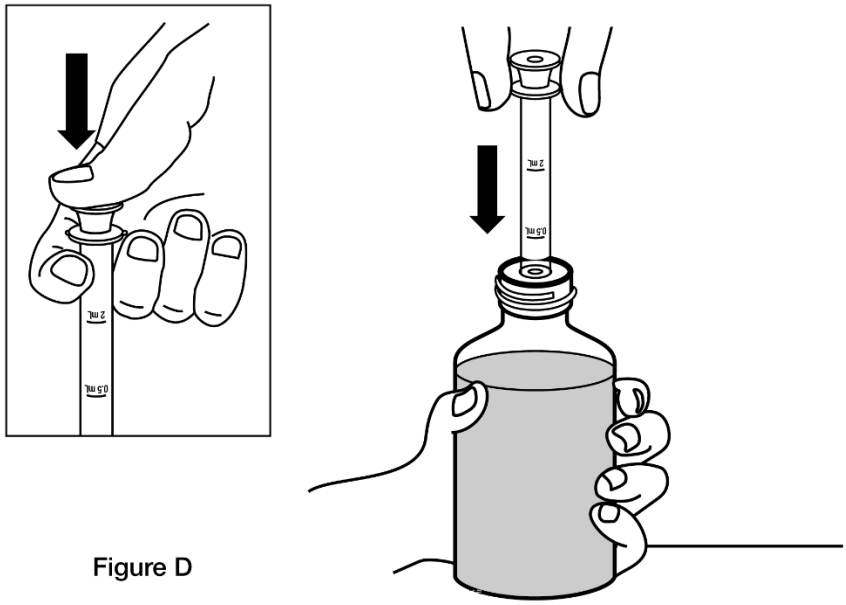

Figure D

Step 4. Turn the bottle upside down while holding the oral dosing syringe in place. Slowly pull back the plunger of the oral dosing syringe until the bottom of the plunger is even with the mL marking on the syringe for your or your child's prescribed dose. (See Figure E)

If your child's dose of REVATIO oral suspension is 1 mL (10 mg), measure 0.5 mL two times for a total of 1 mL of REVATIO oral suspension.

If your or your child's dose of REVATIO oral suspension is more than 2 mL (20 mg), you will need to divide the dose. Follow the instructions given to you by your healthcare provider or pharmacist about how to prepare the divided dose.

If you see air bubbles in the oral dosing syringe, slowly push the plunger all the way up so that REVATIO oral suspension flows back into the bottle and repeat Step 4.

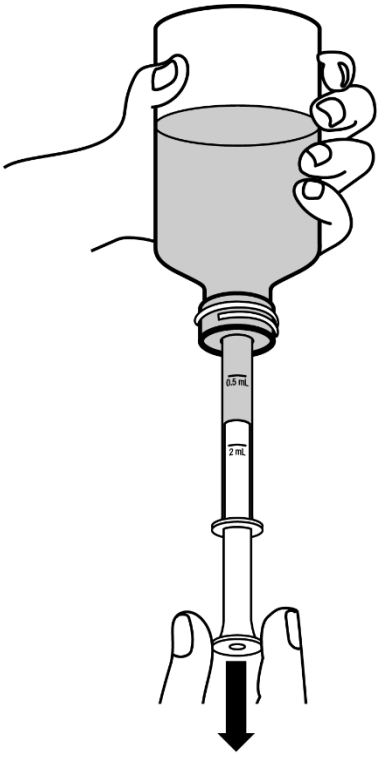

Figure E

Step 5. Turn the bottle back upright with the oral dosing syringe still in place. Place the bottle on a flat surface. Remove the oral dosing syringe from the bottle adaptor by pulling straight up on the barrel of the oral dosing syringe. (See Figure F) **Do not press on the plunger of the oral dosing syringe at this time.**

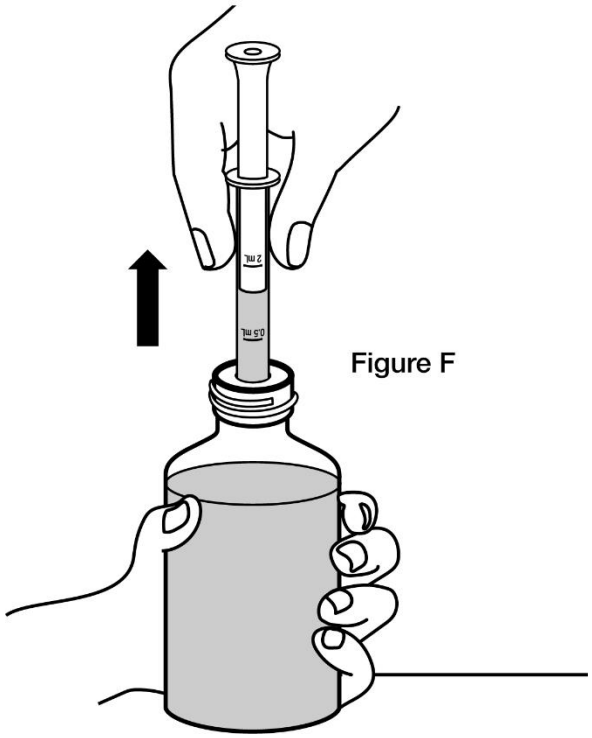

Figure F

Step 6. Put the tip of the oral dosing syringe into your or your child's mouth and point it towards the inside of the cheek. Slowly push the plunger of the oral dosing syringe all the way down to give the entire dose. Do not squirt the medicine out quickly. (See Figure G)

If you are giving REVATIO oral suspension to a child, make sure they are in an upright position before giving the medicine.

Figure G

Step 7. Replace the cap on the bottle, leaving the bottle adaptor in place. Turn the cap in the direction of the arrow (clockwise) to close the bottle. (See Figure H)

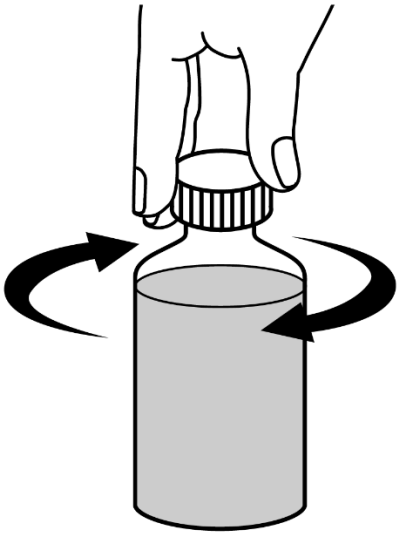

Figure H

Step 8. Wash the oral dosing syringe after each use. Pull the plunger out of the barrel and rinse both parts with water. (See Figure I)

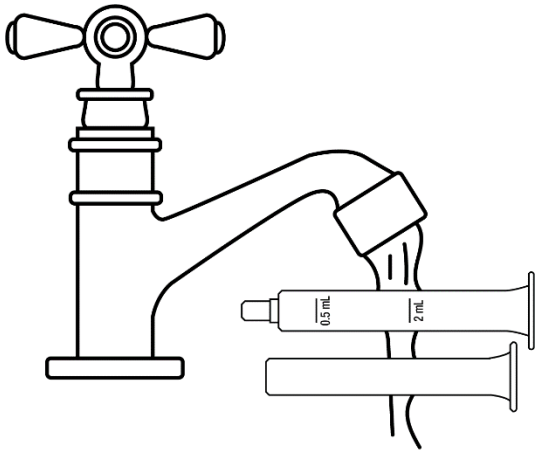

Figure I

Step 9. Dry all parts with a clean paper towel. Push the plunger back into the barrel. Store the oral dosing syringe with the REVATIO oral suspension bottle.

How should I store REVATIO?

- Store mixed (reconstituted) REVATIO oral suspension below 86°F (30°C) or in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze mixed REVATIO oral suspension.
- Throw away (discard) any remaining REVATIO oral suspension 60 days after mixed by the pharmacist. See the "Discard after" date written on the bottle label.

Keep REVATIO and all medicines out of the reach of children.

Distr buted by:
Viatris Specialty LLC, Morgantown, WV 26505 U.S.A.

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This Instruction for Use has been approved by the U.S. Food and Drug Administration. Revised: January 2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021845Orig1s025

CLINICAL and STATISTICAL REVIEW(S)

CLINICAL – STASTICAL JOINT REVIEW

Application Type	Efficacy Supplement
Application Number(s)	021845 (S-025)
Priority or Standard	Standard
Submit Date(s)	03/31/2022
Received Date(s)	03/31/2022
PDUFA Goal Date	01/31/2023
Division/Office	DCN/OCHEN
Reviewer Name(s)	Christine Garnett, PharmD (Clinical Reviewer) Steve Bai, PhD (Statistical Reviewer) Jialu Zhang, PhD (Statistical Team Leader) Fred Senatore, MD, PhD, FACC (Cross Disciplinary Team Leader) Norman Stockbridge, MD, PhD (Division Director)
Review Completion Date	01/31/2023
Established/Proper Name	Sildenafil Citrate
(Proposed) Trade Name	REVATIO
Applicant	Viatris Specialty LLC
Dosage Form(s)	Oral tablets
Applicant Proposed Dosing Regimen(s)	10 mg three times a day for pediatrics patients ≤ 20 kg 20 mg three times a day for pediatric patients >20 kg
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	REVATIO is indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standardized exercise testing, pulmonary hemodynamics thought to underly improvements in exercise

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Glossary

6MWD	six-minute walk distance
AC	advisory committee
AE	adverse event
AR	adverse reaction
BD	Briefing Document
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CCB	calcium channel blocker
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEC	clinical endpoints committee
CFR	Code of Federal Regulations
CI	confidence interval
$C_{max,ss}$	maximum steady state concentration
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPET	cardiopulmonary exercise test
CRDAC	Cardiovascular and renal drug advisory committee
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C_{ss}	steady state concentrations
CTD	connective tissue disease
CYP	cytochrome P450
DMC	data monitoring committee
ECG	electrocardiogram
ERA	endothelin receptor antagonist

eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FMQ	FDA medical query
GCP	good clinical practice
GRMP	good review management practice
HPAH	heritable pulmonary arterial hypertension
HR	hazard ratio
IA	integrated assessment
IC_{50}	concentration at 50% maximum inhibitory effect
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IPAH	idiopathic pulmonary arterial hypertension
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed model for repeated measure method
mPAP	mean pulmonary arterial pressure
NDA	New Drug Application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAH	pulmonary arterial hypertension
PAH-CHD	PAH associated with congenital heart disease
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDE-5	phosphodiesterase type 5
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	post-marketing requirement

POS	powder for oral suspension
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	MedDRA preferred term
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
REMS	risk evaluation and mitigation strategy
RPM	Regulatory Project Manager
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGE	special government employee
SMQ	Standard MedDRA Query
SOC	MedDRA 'System of Organ Class'
SOC	standard of care
TEAE	treatment emergent adverse event
TID	thrice daily
US	United States
USPI	United States prescribing information
VO_2	Oxygen consumption
WHO	World Health Organization
WR	written request

1 Executive Summary

1.1 Product Introduction and Pertinent Background

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase-5 inhibitor. It was originally approved on 03/27/1998 for the treatment of male patients with erectile dysfunction under the tradename VIAGRA (NDA 020895). Sildenafil was contraindicated for concomitant use of nitrates in any form due to potentiation of hypotensive effect of nitrates. Sildenafil was later approved on 06/03/2005 for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity in adults under the tradename REVATIO.

On December 17, 2002, the FDA issued a pediatric Written Request (WR) requiring the Applicant to perform a placebo-controlled trial evaluating either clinical events or functional improvement in pediatric patients with primary or secondary pulmonary hypertension. In response to the WR, the pediatric program was initiated in 2003 with the STARTS-1 trial (a 16-week, randomized, double-blind, placebo-controlled, dose ranging study of oral sildenafil in treatment-naïve children with pulmonary arterial hypertension). This was followed by STARTS-2 (an open label safety extension study with oral sildenafil monotherapy in treatment-naïve pediatric PAH patients).

(b) (4) Study A1481244, a 12-week dose-response study investigating the use of 1 mg, 5 mg and 20 mg TID sildenafil in treating subjects with PAH that was less severe, but where chronic therapy was needed. The primary efficacy endpoint was the 6MWD. Study A1481244 demonstrated an increase in total distance walked in each treatment group during the 6MWD at Week 12 (last-observation-carried forward, intention-to-treat population). The increase was clinically significant in the 5 mg and 20 mg groups (mean changes of 41 meters [95% CI: 25.16, 56.34] and 38 meters [95% CI: 23.77, 52.94], respectively), but smaller and non-clinically significant increases in total distance walked in the 1 mg group.

On July 29, 2010, the Cardiovascular and Renal Drugs Advisory Committee was convened to ascertain whether hemodynamic measurements (i.e., pulmonary vascular resistance index-PVRI, or mean pulmonary arterial pressure-mPAP) may serve as primary efficacy endpoints in pediatric development programs, particularly for the younger population unable to easily exercise. The committee concluded that, for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population. FDA therefore modified the sildenafil pediatric WR to reflect utility of PVRI changes for pediatric extrapolation.

In 2012, the results of STARTS-1 were reported. Pediatric patients (n=235, weight > 8 kg) were randomized to low, medium, or high dose sildenafil or placebo 3x daily for 16 weeks. Low dose was defined as 10 mg 3x daily for subjects weighing greater than 20 kg. Subjects 20 kg or less were not administered 10 mg when defined as the low dose of sildenafil. Medium dose was defined as 10 mg or 20 mg or 40 mg 3x daily for respective weight ranges >8 kg-20 kg, > 20 kg-45 kg, and > 45 kg. High dose was defined as 20 mg or 40 mg or 80 mg 3x daily for the same respective weight ranges. The primary efficacy endpoint was % change from baseline at week-16 in peak oxygen consumption (pVO2) for the combined doses versus placebo, as measured by cardiopulmonary exercise testing (CPET). Secondary efficacy endpoints included hemodynamics and functional class. The study was powered for the 115 children who were able to exercise reliably.

The estimated mean $\pm$ standard error % change in pVO2 for the three combined doses versus placebo was 7.7 $\pm$ 4.0% (95%CI -0.2 ←→15.6%, p 0.056). A treatment effect (pVO2, functional class, mPAP, and PVRI) was evident in the medium and high doses .vs. placebo. The pVO2 increased by 9.7% (95%CI 1.3←→18.0); the PVRI decreased by 22.8% (95%CI 10.1←→34.1). The placebo-corrected decrease in PVRI as well as the placebo-corrected increase in exercise capacity appeared comparable between the adult and pediatric populations, albeit from different trials (see Table 14). The low dose was ineffective.

From the safety perspective, most adverse events were mild-to-moderate in severity, and generally balanced between the arms of the STARTS-1 trial. The most frequently reported adverse events in this 16-week trial were headache, pyrexia, upper respiratory tract infection, vomiting, and diarrhea. Of the 235 subjects enrolled in STARTS-1, 228 completed the trial and 220 continued into STARTS-2.

In 2014, the results of STARTS-2 were reported. Placebo-treated subjects in STARTS-1 were randomized to one of the three drug dosing arms from STARTS-1. All STARTS-2 subjects received $\geq$ 3 years of treatment. In the subset of children who could undergo CPET, the mean percent increases of pVO2 were 9.9, 6.0, and 2.5 for sildenafil low, medium and high dose, respectively. These findings may have occurred by chance because this was a subgroup finding and there was no placebo group. There were no further improvements in $pV0_2$ in STARTS-2 at 1 year after starting sildenafil treatment. Hemodynamics were not collected in STARTS-2.

There were 42 deaths in STARTS-2 (none in STARTS-1). Of these 42 deaths, 28 were on treatment (within 7 days of the last dose) which included 3 in the low dose, 8 in the medium dose and 17 in the high dose. The time course for the on-treatment deaths did not suggest a dose-related increase until after one year of sildenafil treatment Most of the pediatric population who died had idiopathic PAH with WHO functional class III/IV Subjects who died had worse than median STARTS-1 baseline hemodynamic values: 68%, 76%, 68%, and 73% for mPAP, PVRI, cardiac index, and right atrial pressure, respectively. Kaplan-Meier survival rates over 3 years from the start of sildenafil were 94%, 93%, and 88% for subjects randomized to the

low, medium, and high doses, respectively. A total of 87%, 89%, and 80% for the respective low, medium and high doses were known to be alive at 3 years. Hazard ratios for mortality were 3.95 (95%CI 1.46←→10.65) for the high dose .vs. low dose and 1.92 (95%CI 0.65←→5.65) for the medium dose .vs. low dose. The 5-year survival rate for the low, medium, and high doses were 94%, 84%, and 80%, respectively. Based on various analyses, there was uncertainty about the empirical survival/dose relationship. While increased mortality was observed in higher sildenafil doses compared with low dose, there were no apparent safety signals leading to death. The causes of death could not be definitively attributable to sildenafil; they were consistent with progression of PAH disease and heart failure (see- Appendix 13.3). There were noted imbalances of variables defined as prognostic to survival (i.e., etiology of PAH, baseline right atrial pressure, and baseline PVRI). A new pediatric warning was included in the prescribing information because of the observed dose-related effect on mortality observed in STARTS-2.

While there was skepticism in the FDA and in the community about the reliability of the mortality data from the STARTS program, it was considered infeasible to study the issue further in pediatric patients. Thus, FDA issued a PMR for the Applicant to conduct a post-marketing clinical study to investigate the dose-response relationship for sildenafil on mortality in adults with PAH (WHO Group 1), reasoning that it was very unlikely that the relationship could be qualitatively different in adult and pediatric patients.

On September 22, 2014, the A1481324 trial (trial A1481324; NCT02060487) began in fulfillment of the PMR requirement. This was a multinational, multicenter trial to assess the effect of oral sildenafil on mortality in adults with PAH. The trial was conducted at 68 sites in 23 countries. A total of 385 subjects were randomized 1:1:1 to receive Sildenafil 5 mg (low dose), 20 mg (medium dose), or 80 mg (high dose) orally three times daily. The ITT population included adult subjects with PAH (WHO Group 1, idiopathic or secondary to connective tissue disease (CTD) or having undergone surgical repair) and Functional Class II-IV diagnosed 12-months prior to randomization. Randomization was stratified according to PAH treatment at entry (PAH-treatment-naïve vs. on PAH-on treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). The primary efficacy endpoint was time to all-cause mortality. Secondary efficacy endpoints included time to first clinical worsening and 6MWD at 6 months and at 12 months. Clinical worsening was defined as all-cause mortality, non-elective hospitalization for worsening PAH (including right heart failure), initiation of intravenous prostanoids, lung transplantation, or septostomy. The trial was designed to test for the non-inferiority of sildenafil 80 mg vs. 5 mg for mortality; the mortality rate with the 80 mg dose was hypothesized to be no worse than double the mortality rate for the 5 mg dose (non-inferiority margin of 2). The study was expected to have a total duration of 7.7 years to reach the required number of events (143 deaths). On July 01, 2020, the DMC met to review the results of the interim analysis (50% of mortality events had occurred; 72 deaths) and recommended termination of the trial because the noninferiority objective was met for the 80 mg versus 5 mg dose with respect to

mortality. There was an additional safety concern of increased mortality in patients taking the 5 mg dose.

Baseline demographics and characteristics were generally balanced between the arms of the A1481324 trial. Data for the primary efficacy endpoint showed the mortality hazard ratio for 80 mg .vs. 5 mg was 0.51 (99.7%CI 0.22←→1.21, p 0.021). The mortality hazard ratio for 80 mg .vs. 20 mg was 0.74 (99.7%CI 0.30←→1.84, p 0.333). The mortality hazard ratio for 20 mg .vs. 5 mg was 0.68 (99.7%CI 0.31←→1.49, p 0.142). Since the upper limit of the confidence interval was less than 2, the non-inferiority margin was met for the primary efficacy endpoint (80 mg .vs. 5 mg). The Kaplan-Meier survival curve for the intention-to-treat population showed a dose-dependent improvement in survival for the 20 mg and 80 mg doses relative to the 5 mg dose (see Figure 2).

A1481324 trial data for the secondary efficacy endpoints showed a statistically significant attenuation of clinical worsening for the 80 mg dose .vs. 5 mg (HR 0.44, 99.7%CI 0.22←→0.89, p 0.0005). There was an efficacy trend for 80 mg .vs. 20 mg for clinical worsening (HR 0.71, 99.7%CI 0.33←→1.52, p 0.195). There was a statistically significant reduction in clinical worsening for the 20 mg .vs. 5 mg (HR 0.63, 99.7%CI 0.33←→1.21, p 0.035). However, the definition of clinical worsening was modified compared to how it was originally defined. The modified definition of clinical worsening was a composite of disease progression, hospitalization for PAH, and death. Disease progression was defined as a reduction from baseline in the 6MWD test by 15%, confirmed by a 2nd 6MWD test within 2 weeks of the 1st test, and worsening functional class. Using the Mixed-Model-for Repeated Measures technique for comparison of the change in 6MWD from baseline at month 6, there was a dose-dependent increase in 6MWD for the 20 mg and 80 mg doses compared to the 5 mg dose, with a least squares mean difference of 19 meters between the 80 mg and 5 mg doses. At month 12, there was no difference in 6MWD between the 20 mg and 80 mg doses, but there was a least squares mean difference of 21 meters between the 80 mg and 5 mg dose. However, this difference did not meet the pre-specified criteria for significance (see Table 10).

Safety data from the A1481324 trial was based on a mean exposure of 795 days, 843 days, and 933 days for the 5, 20, and 80 mg doses, respectively. There was a linear decrease in the % subjects treated with drug over time, from 100% at month 1 to 0% at month 69 (see Figure 7). The incidence of death was highest at the lowest dose and decreased in dose-dependent manner (26%, 20%, and 15% for the 5 mg, 20 mg, and 80 mg doses, respectively). The incidence of serious adverse events was highest at the lowest dose (51%, 38%, and 40% for the 5 mg, 20 mg, and 80 mg doses, respectively). Similar patterns were observed using the standard MedDRA broad query (see Table 19). The incidence of any treatment emergent adverse event (TEAE) was similar between the arms (88%, 88%, and 90% for the 5 mg, 20 mg, and 80 mg doses, respectively). Some TEAEs increased in incidence at the higher doses: diarrhea (10%, 13%, 16%), headache (20%, 35%, 20%), dizziness (9%, 13%, 14%), and chest pain (5%, 12%,

11%) each for the 5 mg, 20 mg and 80 mg doses, respectively. Some of these trends (headache, dizziness) were likely due to the vasodilatory mechanism of action.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The basis of substantial evidence of efficacy rests with the STARTS-1 trial and extrapolatory data from the A1481324 trial in adults via bridging strategies to the pediatric population.

The STARTS-1 trial was marginally significant for the primary efficacy endpoint (marginal significance defined as barely missing the pre-specified criteria for success). PVRI decreased by a mean of 23%; the placebo-corrected improvement in exercise capacity and placebo-corrected decrease in PVRI were empirically comparable between adults and pediatric patients, albeit the data coming from different trials. The data from the STARTS-1 trial showed an exposure-response relationship for changes from baseline in PVRI at week 16 (i.e., greater magnitude of decreased PVRI with increasing mean steady state concentration of sildenafil-see Figure 6).

The A1481324 trial (in adult PAH subjects) demonstrated a treatment effect by reducing mortality for the 20 mg and 80 mg doses compared to the 5 mg dose. Other treatment effects included a reduction in clinical worsening for the higher doses relative to the 5 mg dose, and an increase in exercise capacity for the 80 mg dose compared to the 5 mg dose.

Given these findings as well as the acceptability of PVRI as a bridging biomarker, it is reasonable to conclude that sufficient evidence was presented to warrant a recommendation to approve the 20 mg and 80 mg dose to treat pediatric patients with PAH in a weight-based dosing strategy: 10 mg TID in patients < 20 kg; 20 mg TID in patients 20 kg to 45 kg; 20 mg TID in patients > 45 kg with options to increase in this subgroup pending symptoms and tolerability.

1.3 Benefit-Risk Assessment

The risk of sildenafil rests with the persuasiveness of the mortality signal observed in the STARTS-2 trial. A concrete explanation for the dose-dependent mortality signal has remained elusive especially in the setting of a mortality benefit at higher doses in the adult population with concomitant improvement in bridging biomarkers to the pediatric population.

Confounders have impacted the ability to adequately interpret the STARTS-2 mortality data such as imbalances in PAH etiology, baseline right atrial pressure, and baseline PVRI. Subjects who died had worse than median STARTS-1 baseline hemodynamic values: 68%, 76%, 68%, and 73% for mPAP, PVRI, cardiac index, and right atrial pressure, respectively. Thus, disease progression may have impacted the mortality of STARTS-2 subjects. Also, medication data were not collected post-withdrawal of sildenafil in STARTS-2 thus attenuating the ability to understand the etiology of the STARTS-2 mortality data.

The overall safety profile of sildenafil was characterized by: 1) balance in adverse events between all the arms of the STARTS-1 trial; 2) no apparent safety signal leading to death in

STARTS-2; and 3) an incidence of serious adverse events that was highest at the low dose of sildenafil suggesting insufficiency of a therapeutic benefit at the low dose.

Given the therapeutic benefit observed in STARTS-1 and A1481324 along with an improvement in PVRI (bridging biomarker) in both adults and pediatric patients and given the elusive etiology of the mortality signal in STARTS-2 based on confounding covariates in the setting of no other safety signal, it may be reasonably concluded that the benefit of sildenafil overrides the risk of sildenafil. Weight-based dosing should be approved for the pediatric population. The 5 mg dose appears ineffective in attenuating adverse events associated with disease progression.

Table 1. Benefit-Risk Assessment for Pediatric PAH

	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition	PAH (World Health Organization Group 1) is a rare, serious, and progressive disease. It is characterized by increased PVR, increased pulmonary artery pressure, and right ventricular dysfunction, which leads to right heart failure, morbidity, and mortality. Both adults and children have the same hemodynamic definition of PAH. Data from the Netherlands in 2011 showed an annual incidence and point prevalence (per million children) of 0.7 and 4.4 for IPAH and 2.2 and 15.6 for PAH-CHD. Pediatric PAH shares common features of adult disease. Both populations have vascular and endothelial dysfunction, and similar histopathology. Children have a greater predominance of IPAH/HPAH and PAH due to congenital heart disease. Children with PAH appear to have more similarities in disease characteristics to adults with PAH than differences.	PAH in children is rare, serious, and progressive disease with significant morbidity and mortality. The disease in children is similar to the adult disease such that pediatric development programs for drugs shown to be effective in adults can rely on pediatric extrapolation approaches.
Current Treatment Options	Bosentan is the only drug approved in the US for children and adolescents, 3-18 years, but can cause liver injury and close monitoring of liver function is needed. Drugs approved in adults are extensively used off-label in children, including sildenafil. Registry databases have shown improved survival rates in children taking off-labeled PAH-specific therapies.	Pediatric PAH remains an area of unmet medical need. No treatments approved for children under 3 years. Therapeutic algorithms in children are based on expert opinion and evidence-based adult studies. There are limit randomized, controlled trials in pediatrics.
Benefits in Children	STARTS-1 failed to show a significant effect of sildenafil on the primary endpoint in the subset of children who were developmentally able to exercise (n=115). The combined doses (low, medium and high) produced a statistically insignificant 7.7 % increase in the peak VO_2 treatment effect (p=0.056).	The STARTS-1 trial was marginally significant for the primary efficacy endpoint. PVRI decreased by a mean of 23%; the placebo-corrected improvement in exercise capacity and placebo-corrected decrease in PVRI were empirically comparable between adults and pediatric patients, albeit the data coming from different trials. The data from the STARTS-1 trial showed an

<table>
<tr><th></th><th>Evidence and Uncertainties</th><th>Conclusion and Reasons</th></tr>
<tr><td></td><td>The low dose group produced sildenafil concentrations below the intended effective concentration level which was targeted to be higher than IC_{50} for inhibition of PDE-5.

Exposure-response analyses for PVRI and peak VO_2 supports the efficacy of the medium and high sildenafil doses.

Pooled Medium and High sildenafil doses were associated with improved exercise capacity, WHO functional class, hemodynamic parameters (PVRI, mPAP) and parent/physician global assessments at Week 16.

<table>
<tr><th>Benefit*</th><th>Treatment Effect
(95% CI)</th></tr>
<tr><td>Increase in peak VO_2</td><td>9.7% (1.3, 18.0)</td></tr>
<tr><td>Decrease in PVRi</td><td>22.8% (10.1, 34.1)</td></tr>
<tr><td colspan="2">*Based on post-hoc analysis of pooled Medium and High dose groups in pediatrics in STARTS-1.
Medium dose group gives sildenafil exposures in children and adolescents similar to those in adults taking 20 mg TID.</td></tr>
</table>

Both the pediatric and adults had similar treatment effect on PVRI [22.8% reduction in pediatrics in STARTS-1 vs. 21.2% reduction in adults in Study A1481140]. The improvement in PVRI in STARTS-1 is consistent with the change in peak VO2 being clinically relevant because changes in PVR correlates with changes in exercise capacity as measured by the 6-minute walk test in adults with PAH.

This is further supported by comparing the effects of sildenafil on exercise capacity. The percent increase in peak V02 in children at the medium and high doses is similar to the percent increase in 6-minute walk distance in</td><td>exposure-response relationship for changes from baseline in PVRI at week.

Given these findings as well as the acceptability of PVRI as a bridging biomarker, it is reasonable to conclude that sufficient evidence was presented to warrant a recommendation to approve the 20 mg dose to treat pediatric patients with PAH.</td></tr>
</table>

<table>
<tr><th></th><th>Evidence and Uncertainties</th><th>Conclusion and Reasons</th></tr>
<tr><td></td><td>adults [9.7% increase in pediatrics in STARTS-1 vs. 13.1% increase in adults in Study A1481140].</td><td></td></tr>
<tr><td>Risks and Risk Management</td><td>There was an apparent dose-response for mortality in pediatric population in STARTS-2.
<table>
<tr><th>Risk*</th><th>Treatment Effect for Low, Medium, High</th></tr>
<tr><td>3-y survival rate</td><td>0.94, 0.93, 0.88</td></tr>
<tr><td>5-y survival rate</td><td>0.94, 0.84, 0.80</td></tr>
<tr><td colspan="2">*from the start of treatment in STARTS-1. Includes both on- and off-treatment deaths</td></tr>
</table>
Uncertainties in the dose-response for mortality include:

The time course for the on-treatment deaths do not suggest a dose-related increase until after one year of sildenafil treatment. Off-treatment deaths occurred between 9 days to 1202 days (median: 217 days) of the last sildenafil dose.
Although 56% subjects had up-titrations in the low dose group after year 1, the deaths in this group remained low.
There was no apparent safety signal leading to death. The causes of death did not indicate a specific drug-related cause and were consistent with progression of PAH disease and heart failure.
There was also no pattern in the adverse events, laboratory findings, vital signs, ECGs or discontinuations that suggests a drug-related cause to the mortality events.
Post-marketing safety data have not revealed any new safety findings in pediatrics.
</td><td>There are now mitigating data that puts into question the mortality signal in STARTS-2:

A1481324 showed controlled, long-term survival benefit in a related adult population with PAH (i.e., newly diagnosed, treatment naïve, IPAH/HPAH etiology)

The 3- and 5-year survival rates in pediatrics at all dose levels was not worse than the survival rates in A1481324 (Figure 13).

Long term positive effects on reducing rate of disease worsening and improvement in exercise capacity were noted in A1481324.
There was no corroborating safety signal for death in over 10 years clinical experience with off-label use of sildenafil in the pediatric population, and in ex-US post-marketing safety experience.
</td></tr>
</table>

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1 Analysis of Condition

Pulmonary arterial hypertension (PAH) is a rare and serious disease characterized by increased pulmonary vascular resistance (PVR), increased pulmonary artery pressure, and right ventricular

dysfunction, which often leads to right heart failure, morbidity and mortality. The earliest symptom, in most cases of PAH, is the gradual onset of shortness of breath after physical exertion. Other symptoms include chest pain, near syncope or syncope, fatigue, and peripheral edema. There are a number of treatments available for PAH in adults including phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (bosentan, macitentan, ambrisentan), prostanoids (epoprostenol, treprostinil, iloprost), prostacyclin receptor agonist (selexipag) and soluble guanylate cyclase stimulators (riociguat).

Pediatric PAH shares common features of the adult disease (Group 1 pulmonary hypertension): children have the same hemodynamic profile as adults and similar vascular and endothelial dysfunction (Barst 2011).[1] The distribution of PAH etiologies are, however, different whereby children have a greater predominance of idiopathic PAH (IPAH), PAH associated with congenital heart disease (PAH-CHD) and developmental lung diseases (Rosenzweig 2019).[2]

Clinical presentations in children and adults are similar and are characterized by an increased right ventricular workload, right heart failure, and impaired left heart filling. The most frequent presenting symptoms in both children and adults include dyspnea on exertion and fatigue, near-syncope, syncope, and chest pain. Although children have more syncope and less heart failure and edema than adults (Barst 2011)[1], clinical experts have agreed that there are more similarities in disease characteristics than differences.

2.2 Analysis of Current Treatment Options

Due to the lack of controlled clinical trials in children with PAH, this disease remains an area of unmet medical need. In the US, bosentan is indicated for the treatment of PAH (WHO Group 1) in pediatric patients ages 3 years and older with idiopathic or congenital PAH. Bosentan is an endothelin receptor antagonist and was shown to improve PVR, which is expected to result in an improvement in exercise ability. Bosentan is associated with significant elevations of liver aminotransferases/liver abnormalities and requires close monitoring of liver function.

Treatment strategies in children are based on experience with off-label use of drugs approved in adults (Figure 1). Off-label treatment of oral PAH-targeted therapy in children with lower-risk PAH is recommended (Class I; Level of Evidence B) in treatment guidelines developed by

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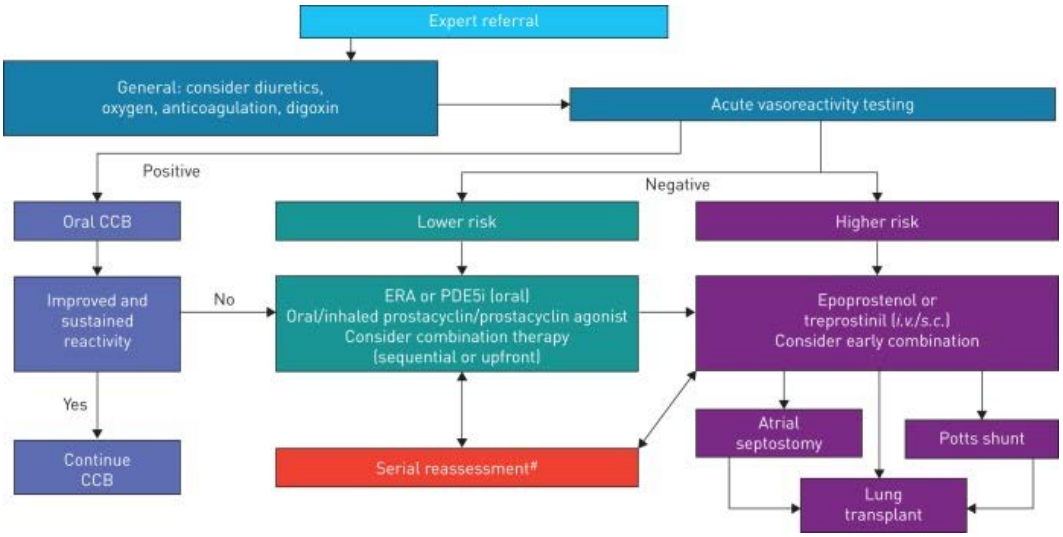
[1] Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J. 2011;37(3):665-677. doi:10.1183/09031936.00056110

[2] Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):1801916. Published 2019 Jan 24. doi:10.1183/13993003.01916-2018

American Heart Association and American Thoracic Society and includes either a phosphodiesterase type 5 inhibitor (PDE-5i), such as sildenafil or tadalafil, or an endothelin receptor antagonist (ERA), such as bosentan or ambrisentan (Abman 2016).[3] Sildenafil is usually preferred over tadalafil by most centers for this indication because published studies show favorable responses (Avitabile 2020).[4] Sildenafil doses are limited to 20 mg TID after the FDA issued a safety warning for high doses of sildenafil based on the STARTS-2 trial.[5] Current treatment guidelines also recommend the initiation of combination therapies in children with higher risk, such as a combination PDE-5i + ERA.

Figure 1. Pediatric PAH Treatment Algorithm



[Abbreviations: CCB, calcium channel blocker; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase type 5 inhibitors. Source: Rosenzweig 2019[6]]

[3] Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society [published correction appears in Circulation. 2016 Jan 26;133(4):e368]. Circulation. 2015;132(21):2037-2099. doi:10.1161/CIR.0000000000000329

[4] Avitabile CM, Vorhies EE, Ivy DD. Drug Treatment of Pulmonary Hypertension in Children. Paediatr Drugs. 2020;22(2):123-147. doi:10.1007/s40272-019-00374-2

[5] FDA Drug Safety Communication. December 15, 2017. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-recommends-against-use-revatio-sildenafil-children-pulmonary

[6] Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):1801916. Published 2019 Jan 24. doi:10.1183/13993003.01916-2018

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate-specific PDE-5. It was originally approved on 03/27/1998 for the treatment of male patients with erectile dysfunction under the tradename VIAGRA. It was later approved on 06/03/2005 for the treatment of PAH to improve exercise ability in adults under the tradename REVATIO.

FDA issued a pediatric Written Request (WR) on 12/17/ 2001 which required the Applicant to perform a controlled trial measuring either clinical events or functional improvement in which oral sildenafil and placebo are each added to standard therapy in pediatric patients with primary or secondary pulmonary hypertension (Study A1481131, STARTS-1) followed by an open-label safety extension study (Study A1481156, STARTS-2). The pediatric development program was initiated in 2003.

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) was convened on 07/29/2010 to discuss the potential use of the hemodynamic measurements as primary endpoint for the efficacy portion of the pediatric development program, particularly for the younger population unable to easily exercise. The advisory committee indicated that a hemodynamic endpoint given the correlation of pulmonary vascular resistance index (PVRI) or mean pulmonary arterial pressure (mPAP) and walk performance would be acceptable. As a result, the FDA changed the pediatric WR to evaluate PVRI as the main efficacy variable.

The Applicated submitted the pediatric studies A1481131 (STARTS-1) and A1481156 (STARTS-2) to support a pediatric indication on 11/30/2011. During the review, safety concerns were identified within the STARTS-2 study, as there was a dose-response increase in mortality of patients. The pediatric formulation was approved on 08/30/2012 and the FDA added a new pediatric warning for dose-related effect on mortality.

The FDA issued a PMR to conduct one or more post-marketing clinical studies to investigate the long-term effects of multiple doses of sildenafil on mortality in adults with PAH (WHO Group 1). Study A1481324 was designed to fulfill this PMR. Summary of Presubmission/Submission Regulatory Activity

- FDA held an informal teleconference with Applicant to discuss the results from study A1481324 on 06/7/2021. During this meeting, Applicant and FDA aligned on plans to submit a sNDA to 021845 proposing the use of sildenafil in pediatric patients (1 to 17 years of age) with PAH (b) (4) (b) (4) based on the final results of study A1481324.

- FDA and Applicant held a Type B, pre-NDA meeting on 11/4/2021 to discuss the final structure, content, format, and data presentation of a sNDA submission for a new indication – the treatment of pediatric PAH.
- FDA and Applicant held a teleconference on 12/15/2021 to align on 2 statistical issues that were raised during the pre-NDA meeting.
    - There was agreement to not include (b) (4) (b) (4)
    - FDA agreed that in absence of a pre-specified hierarchical testing procedure, retrospective proposal of multiplicity testing that is potentially free of bias can be difficult. Whether clinical worsening can be included in the US Prescribing Information (USPI) will ultimately be a review issue. FDA recommended to include scientific justification on the relevance of this information to prescribers, clinicians, and patients.

3.2 Foreign Regulatory Actions and Marketing History

Sildenafil tablets and powder for oral suspension (POS) are approved for treatment of pediatric PAH patients, ages 1-17 years, in Europe since 2011, Japan since 2017 and Indonesia since 2019.

Reviewer's Comment: Pfizer updated the Summary of Product Characteristics in Europe in September 2011 to include pediatric mortality data from the long-term extension Study A1481156 (STARTS-2) to reinforce the dosing recommendations for this population, and to introduce a warning that higher than recommended doses should not be used in pediatric patients with PAH.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Clinical site inspections were not conducted. None of the sites enrolled more than 10% of the total population. Statistical analysis of the primary endpoint by site showed that none of the sites had an influence on the overall results.

4.2 Product Quality

No new product quality data were submitted.

4.3 Clinical Microbiology

Not applicable.

4.4 Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted.

4.5 Clinical Pharmacology

No new clinical pharmacology data were submitted.

4.6 Devices and Companion Diagnostic Issues

Not applicable.

4.7 Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

The clinical studies referenced in this review are shown in Table 2. The post-marketing safety study A1481324 was submitted in the current efficacy supplement.

Pediatric studies A1481131 (STARTS-1) and A1481156 (STARTS-2) were previously submitted and reviewed in 2012 under NDA 203109, sNDA 021845/S-008, and sNDA 022473/S-003. These studies support the proposed indication and benefit-risk assessment; therefore, key findings are summarized in sections 6.2 (efficacy) and 8.2.2 (safety).

Table 2. Listing of Clinical Trials Relevant to this Application

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Study in Adult PAH Population						
A1481324	NCT02060487	Randomized, double-blind, parallel-group study in adult subjects with PAH that was designed to assess mortality during long-term treatment with sildenafil at 3 doses. *Note: The DMC met to review the results of the interim analysis (50% of mortality events had occurred; 72 deaths) on 01 July 2020 and recommended to stop the study.*	Sildenafil (5, 20, or 80 mg) orally three times daily	Primary: time to death (all-cause); Secondary: time to first clinical worsening event and six-minute walk distance	The study was expected to have a total duration of 7.7 years to reach the required number of events (143 deaths).	385 subjects were randomized: 129 (5 mg TID), 128 (20 mg TID) and 128 (80 mg TID)	Adult subjects with PAH (WHO Group 1); Functional Class II-IV; 12-months since diagnosis	68 centers in 23 countries
		Studies in Pediatric PAH Population (previously submitted and reviewed)						
A1481131 STARTS-1[7]	NCT00159913	Randomized, double-blind, multi-center,	Placebo or sildenafil doses	Primary: maximal VO2;	16 weeks	234 patients randomized:	Pediatric subjects with body weight ≥8	32 centers in 16

[7] Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 2012;125(2):324-334. doi:10.1161/CIRCULATIONAHA.110.016667

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		placebo controlled parallel group, dose ranging study. The study included subjects, aged 1 to 17 years with body weight ≥8 kg, and with primary PAH, or PAH secondary to congenital heart disease including those who had a surgical repair ≥6 months prior to screening, or collagen vascular disease.	based on body weight (low-10 mg, medium 10-40 mg or high 20-80 mg), orally three times daily.	Secondary: hemodynamics, WHO functional class		60 (placebo), 42 (low dose), 55 (medium dose), 77 (high dose)	kg, and with primary PAH, or PAH secondary to congenital heart disease including those who had a surgical repair ≥6 months prior to screening, or collagen vascular disease	countries
A1481156 STARTS-2[8]	NCT00159874	Multicenter, long-term extension study to assess safety of oral sildenafil in the treatment of subjects who have completed study A1481131	Sildenafil doses based on body weight (low-10 mg, medium 10-40 mg or high 20-80 mg), orally three times daily	Primary: Safety Secondary: exercise capacity at Year 1, WHO functional class	Median treatment exposure across all patients was 4.1 years (range, 3 days to 7.4 years)	228 subjects completed STARTS-1, of which 220 subjects entered STARTS-2	Same as in STARTS-1	32 centers in 16 countries

[8] Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014;129(19):1914-1923. doi:10.1161/CIRCULATIONAHA.113.005698

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5.2 Review Strategy and Key Review Issues

In 2011, the Applicant submitted a NDA for a new dosage form (powder for oral suspension) and the application contained efficacy and safety data from pediatric studies STARTS-1 and STARTS-2 which evaluated weight-based dosing (low, medium and high; see Table 11). During the review, safety concerns were identified in the uncontrolled, long-term extension STARTS-2 study, as there was an observed dose-response increase in mortality of patients. As a result, a new pediatric warning was included in the prescribing information because of the observed dose-related effect on mortality observed in STARTS-2. FDA issued a PMR for the Applicant to conduct a post-marketing clinical study to investigate the effects of multiple doses of sildenafil on mortality in adults with PAH (WHO Group 1).

The post-marketing safety study (A1481324) was designed to test for the non-inferiority of sildenafil 80 mg vs. 5 mg for mortality; the mortality rate with the 80 mg dose was hypothesized to be no worse than double the mortality rate for the 5 mg dose. This study was a randomized, double-blind, parallel-group study in 429 adult subjects with PAH (WHO Group 1). Subjects were randomly assigned on a 1:1:1 basis to either blinded sildenafil 5 mg TID, 20 mg TID or 80 mg TID at the baseline visit (Day 1) after successfully fulfilling all inclusion and exclusion criteria. Randomization was stratified according to PAH treatment at entry (PAH-treatment-naïve vs. on PAH-treatment) and etiology of PAH (idiopathic vs. secondary to connective tissue disease (CTD)/surgical repair). Blinded sildenafil treatment continued for the duration of the subject's participation in the study. Based on the recommendation of the Data Monitoring Committee (DMC), the study was stopped early when the protocol-planned interim analysis (50% deaths; triggered by the death of the 72nd patient) showed the noninferiority objective was met for the 80 mg versus 5 mg dose with respect to mortality. There was an additional safety concern of increased mortality in patients taking the 5 mg dose.

Key review issues are:

1. Whether the non-inferiority mortality results for the 20 mg and 80 mg TID dosing regimens in A1481324 in adult patients with PAH mitigates the safety concern for the apparent dose-response increase in deaths in the pediatric PAH population.
2. Whether it is reasonable to conclude, based on the available data, that sildenafil has a favorable benefit-risk assessment to be used for the treatment of PAH (WHO Group 1) in pediatric patients, 1 to 17 years.

(b) (4)

5.3 Data Sources

Study A1481324 (A1481324): The Applicant's electronic data sources were stored in the directories of \\CDSESUB1\evsprod\nda021845\0244\ of the Center's electronic document

room. Data sources include all material reviewed, i.e., study reports, raw data sets in SDTM format, analysis data sets in ADaM format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc.

Study A1481156 (STARTS-2, final datasets): The Applicant's electronic data sources were stored in the directories of \\CDSESUB1\evsprod\NDA203109\0052\ of the Center's electronic document room. These datasets are the final data for STARTS-2; previous FDA reviews were based on an interim dataset.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1 Study A1481324

6.1.1 Study Design

Overview and Objective

A1481324 was designed to fulfil the PMR issued by the US FDA to evaluate the effect of sildenafil on the risk of death in adults with PAH at 3 dose levels: sildenafil 5 mg TID, sildenafil 20 mg TID, and sildenafil 80 mg TID (see Regulatory History, section 3).

A1481324 was designed to test for the non-inferiority of sildenafil 80 mg vs. 5 mg for mortality; mortality rate with the 80 mg dose hypothesized to be no worse than double the mortality rate for the 5 mg dose.

Trial Design

This was a randomized, double-blind, parallel-group study in 429 adult subjects with PAH (WHO Group 1).

Subjects were randomly assigned on a 1:1:1 basis to either sildenafil 5 mg TID, 20 mg TID or 80 mg TID at the baseline visit (Day 1) after successfully fulfilling all inclusion criteria and not meeting exclusion criteria. Randomization was stratified according to PAH treatment at entry (PAH-treatment-naïve vs. on PAH-treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). Blinded sildenafil treatment continued for the duration of the subject's participation in the study.

> *Reviewer's comment: The 5 mg TID dose was chosen to evaluate whether doses lower than the recommended dose of 20 mg TID might be similarly effective and relatively safer when used for the long-term treatment of adult PAH. Although the current US label does not recommend sildenafil at doses above 20 mg TID, it is known from prescribing practices that some adults with PAH are prescribed doses up to 80 mg TID.*

Subjects who discontinued from the study continued to be followed for the primary endpoint. Specified clinical events were reviewed on an ongoing basis by a clinical endpoints committee (CEC) to determine if endpoint criteria were met. Planned interim analyses to test the hypothesis of non-inferiority were to be performed for primary comparison of 80 mg vs. 5 mg when approximately 50% and 75% of mortality events had occurred.

Study data (mortality rate, clinical worsening and safety data) were monitored by an independent DMC to safeguard the interest of study subjects. The DMC met on a regular basis

and provided recommendations on the conduct of the study, including stopping the study, if necessary. The DMC also met after each interim analysis.

With 429 subjects (143 subjects in each treatment group), the study was powered at 90% to test the hypotheses that the 80 mg dose is no worse than double the mortality rate for the 5 mg dose at overall significance level of 0.025 (1-sided). The study was expected to complete enrollment in about 4.3 years with total duration of about 7.7 years to reach required number of events (deaths) of 143.

Key Inclusion and Exclusion Criteria

The study enrolled adult subjects (≥18 and <75 years of age) with Group 1 PAH:

a. Idiopathic Pulmonary Arterial Hypertension (IPAH); or

b. PAH secondary to CTD; or

c. PAH with surgical repair (at least 5 years previously) of atrial septal defect, ventricular septal defect, patent ductus arteriosus and aorto-pulmonary window.

PAH must have been newly diagnosed (confirmed by right heart catheterization) within 12 months prior to randomization (mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤15 mmHg, and PVR >4 mmHg/L/min or 320 dynes*sec/cm^5).

Subjects had WHO Functional Class II-IV and baseline 6MWD ≥50 meters.

Subjects had no prior long term PDE-5 inhibitor treatment. Prior episodic use of PDE-5 inhibitors for erectile dysfunction or prior limited trial use (maximum of 4 weeks) provided that PDE-5 inhibitor was not discontinued for lack of efficacy.

Subjects were excluded if they had PAH secondary to other etiologies than those listed for study inclusion; were being treated with bosentan or riociguat within 3 months of randomization or were currently treated with nitrates or nitric oxide or were taking a new therapy for PAH <3 months prior to randomization or change in background treatment specific for PAH within 30 days prior to randomization.

> *Reviewer's comment: The inclusion/exclusion criteria are acceptable and protocol treatment is appropriate for the subjects enrolled into the trial.*

Study Endpoints

- Primary Efficacy: Time to death (all-cause)
- Secondary Efficacy:
    - Time to (first event of) clinical worsening defined as a composite of all-cause mortality; non-elective hospital stay for worsening PAH (including but not limited

to right heart failure, initiation of IV prostanoids, lung transplantation, or septostomy); or disease progression [defined as a reduction from baseline in the 6MWD test by 15%, confirmed by 2nd test done within 2 weeks (could not be performed on same day), and worsening functional class].

- 6MWD at Months 6 and 12

- Tertiary Efficacy:
  - 6MWD at Month 18 and beyond
  - Borg Dyspnea scale
  - WHO pulmonary hypertension functional class

Reviewer's comment: In PAH clinical trials, both 6MWD and time to first clinical worsening event have been used as the primary clinical endpoints to demonstrate efficacy for new PAH therapies. Study's tertiary endpoints were not part of the study protocol but were described in the statistical analysis plan (SAP) Version 2.

Adjudication of clinical endpoints

All deaths, hospitalizations and suspected clinical worsening events were sent to the CEC which was blinded to study treatment. For deaths, the CEC determined cause of death and categorized the cause into the following groups: PAH, Cardiovascular, Non-cardiovascular or Cannot be Determined.

Statistical Analysis Plan

The analysis plan was finalized on March 24, 2021. No major modification of the primary endpoint definition and/or its analysis occurred after protocol finalization dated on November 18, 2014.

Primary Efficacy Endpoint Analysis

The primary objective for the study was to test for the non-inferiority of sildenafil 80 mg TID vs. 5 mg TID for mortality; mortality rate with the 80 mg TID was no worse than double the mortality rate for the 5 mg TID.

The hypotheses for the primary endpoint of mortality were:

H_0: hazard ratio (80 mg TID /5 mg TID) >=2;

H_1: hazard ratio (80 mg TID /5 mg TID) <2.

The hypotheses were tested at an overall level of 2.5% (1-sided). Additional treatment comparisons for 80 mg vs 20 mg, and 20 mg vs. 5 mg was performed where these were considered secondary comparisons. There was no p-value adjustment for multiplicity. If the 1-sided upper confidence limit of the hazard ratio (HR) was less than 2, then the null hypothesis that the mortality rate in the 80 mg is worse than double the rate in 5 mg would be rejected. In

case the hazard ratio was statistically significantly less than 1, then superiority of 80 mg over 5 mg would be claimed. The primary efficacy analysis was conducted using intent to treat (ITT) population, which consisted of all randomized patients treated with study treatment.

For time to death, treatment comparison was conducted using Cox proportional hazard regression model stratified by PAH treatment at entry of the study (PAH-treatment naïve vs. on PAH treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). The estimate of the HR for treatment (sildenafil 80 mg TID/5 mg TID, 80 mg/20 mg TID, and 20 mg TID/5 mg TID) together with its confidence interval (CI) and p-value were provided. Of note, treatment comparisons for 80 mg vs. 20 mg, and 20 mg vs. 5 mg were considered secondary analyses of the time to death endpoint with no p-value adjustment specified.

Secondary Efficacy Endpoints Analyses

There was no p-value adjustment for secondary endpoints analyses.

Secondary endpoint (1): Time to first event of clinical worsening

Analysis: Cox proportional hazard model, analyses using Kaplan-Meier method described above was used for time to first event of clinical worsening. The analyses were done using the ITT population for overall subjects and by randomization stratification factors.

Secondary endpoint (2): 6MWD

Analysis: For change from baseline at Month 6 and Month 12, treatment comparisons were conducted using the mixed model for repeated measure method (MMRM) with covariates of baseline value, treatment and randomization stratification factors. Least square mean difference, its 95% CI and p-value were tabulated for each treatment comparison (sildenafil 80 mg TID vs. 5 mg TID, 80 mg TID vs. 20 mg TID and 20 mg TID vs. 5 mg TID).

Handling of Missing Data

Missing data w imputed. For 6MWD at Month 6 and 12, MMRM was used for statistical analyses for treatment comparisons. For MMRM, all available data in Month 6 and 12 was included in the analyses and any missing data were assumed missing at random.

Interim Analysis

Two interim analyses were planned after 50% and 75% of the required number of events (143 deaths) have occurred. O'Brien-Fleming approach was used for decision making, i.e., reject H_0 with 1-sided p-value <0.0015, and <0.0092 for the interim analyses with 50% and 75% of the mortality events, respectively. The final p-value for rejecting H_0 was <0.022 (1-sided). The planned interim analysis was conducted after 50% of the required number of events (72 deaths) occurred. The DMC reviewed the results of the interim analysis based on the primary

efficacy endpoint of time to death and recommended that the study be stopped as the primary objective (non-inferiority of the 80 mg TID arm vs 5 mg TID arm) had been met. The DMC also expressed a concern regarding the mortality in the 5 mg TID arm. The Applicant accepted the DMC recommendation; all participating sites were notified of DMC recommendation and the end of study activities were initiated. Treatment unblinding to study team members, investigators and subjects and final analyses were done after the database lock.

> *Reviewer's comment: The SAP was amended on 03/24/2021, and before database lock on 04/01/2021. Changes were made to (1) implement protocol amendment 1 and amendment 2; and (2) add secondary and tertiary endpoints and analyses after Blind Data Review 1 (08/19/2019).*

Protocol Amendments

The original protocol (dated 09/25/2013) was amended 2 times: Amendment 1 (dated 11/18/2014) and Amendment 2 (dated 08/28/ 2020).

Amendment 1 to the protocol was issued to implement the following changes:

- Incorporations of revisions previously implemented as Protocol Administrative Change Letters.
- Clarification of secondary endpoint assessment for progression of disease.
- Clarification of inclusion/exclusion criteria.
- Permit short term PDE-5 inhibitor use prior to enrollment.
- Allow temporary discontinuation (up to 14 days) of study treatment to permit temporary treatment with prohibited medications for comorbidities.
- Addition of riociguat as a prohibited medication.
- Implementation of multiple country regulatory agency requests.
- Incorporation of updated company template adverse event (AE) and publication language.
- Correction of inconsistencies and typographical errors.

Amendment 2 to the protocol was issued to implement the following changes after the DMC recommendation to stop the study:

- Addition of Appendix 6: Continuity of study treatment and dose adjustment (5 mg to 20mg TID) in Ukraine, Russia, Czech Republic, Bosnia and Herzegovina, and Mexico
    - To ensure continuity of treatment with sildenafil for subjects in these countries, until they can transition to a program that will provide access to prescription sildenafil at the time of the End of Treatment study visit.
    - To increase, in a blinded manner, the dose for subjects receiving 5 mg TID to 20 mg TID, the approved dose in these 5 countries.

6.1.2 Study Results

Compliance with Good Clinical Practices

All 68 clinical centers were compliant with Good Clinical Practice, incorporating an informed consent that was reviewed and approved by the Independent Ethics Committee or Institutional Review Board before its use. The conduct of the study was supervised by the DMC. Specified clinical events were reviewed on an ongoing basis by a CEC to determine if endpoint criteria were met.

There were 48 of the 68 sites that terminated prematurely. Reasons for terminations included: retirement of Principal Investigator, enrollment issues, and lack of site staff. A terminated site was defined as a site where screened/enrolled/randomized subjects signed an informed consent document, but recruitment of new subjects at the site was stopped prematurely, with no intention of reinitiating recruitment at the site.

There were no site-specific concerns that drove site selection for OSI inspections.

Financial Disclosure

Financial disclosure information is provided (Appendix 13.2).

> *Reviewer's comment: None of the investigators reported receiving compensation from the Applicant.*

Patient Disposition

A total of 445 subjects were screened and 385 subjects were randomized across 68 sites in 23 countries. All 385 subjects received at least one dose of study treatment and constituted the ITT population.

> *Reviewer's comment: 60 screened subjects were not randomized: 47 failed to meet I/E criteria and 13 were not screen failures but were not randomized. Reasons included death, study terminated by sponsor, study withdrawal by subject and unknown reason.*

No subject completed the study in any treatment group because the study was terminated by the Applicant after the completion of the first interim analysis.

During the active double-blind treatment period, 85% of subjects discontinued from the study and from study treatment at the same time. The most common reason for study discontinuation was death (with the exception of the study termination by the Applicant), the percentage of deaths was highest in the sildenafil 5 mg TID group. Subjects who discontinued from the treatment continued to be followed for the primary endpoint.

Prior to the Applicant terminating the study, an additional 15% of subjects discontinued from treatment but continued to be followed off treatment in the post-treatment follow-up period. The most common reason for study discontinuation was death (with the exception of the study termination by the Applicant).

Table 3. Study A1481324 Disposition

	Sildenafil 5 mg (N=129)	Sildenafil 20 mg (N=128)	Sildenafil 80 mg (N=128)	Total (N=385)
Withdrawn During Active/Double Blind Treatment **Period**				
Discontinued	**105 (81.4)**	**106 (82.8)**	**115 (89.8)**	**326 (84.7)**
Reason for discontinuation				
Adverse event	0	0	1 (0.8)	1 (0.3)
Death	28 (21.7)	17 (13.3)	16 (12.5)	61 (15.8)
Insufficient clinical response	0	1 (0.8)	0	1 (0.3)
Lost to follow-up	3 (2.3)	0	1 (0.8)	4 (1.0)
Other	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.8)
Protocol deviation	0	1 (0.8)	0	1 (0.3)
Screen failure	1 (0.8)	0	0	1 (0.3)
Study terminated by sponsor	70 (54.3)	79 (61.7)	92 (71.9)	241 (62.6)
Withdrawal by subject	2 (1.6)	7 (5.5)	4 (3.1)	13 (3.4)
Completed	0	0	0	0
Withdrawn During Post-Therapy Follow-Up **Period**				
Discontinued	**24 (18.6)**	**22 (17.2)**	**13 (10.2)**	**59 (15.3)**
Reason for discontinuation				
Death	6 (4.7)	8 (6.2)	3 (2.3)	17 (4.4)
Lost to follow-up	0	0	1 (0.8)	1 (0.3)
Other	0	1 (0.8)	0	1 (0.3)
Protocol deviation	0	0	1 (0.8)	1 (0.3)
Study terminated by sponsor	17 (13.2)	10 (7.8)	8 (6.2)	35 (9.1)
Withdrawal by subject	1 (0.8)	3 (2.3)	0	4 (1.0)
Completed	0	0	0	0

[Source: Reviewer's results]

Protocol Violations/Deviations

The most common protocol deviations were those related to procedures/tests deviations (64-66%) and visit schedule (30-32%) which occurred during the COVID pandemic—Dear Investigator Letter was sent on 03/23/2020 to inform sites that monitoring visits were suspended. Protocol deviations related to the investigational product included subjects who

had deviations in drug accountability (i.e., documentation of receipt and amounts dispensed to and returned by study subjects).

Reviewer's comment: During the Covid-19 pandemic, monitoring visits were conducted by phone, study treatment was shipped subjects, and local labs were used for blood tests. These were documented as protocol deviations.

Demographic Characteristics

All 3 treatment groups were balanced with respect to baseline demographics, history of PAH treatment and etiology of PAH (Table 4).

Overall, subjects were predominantly female (77%), white (84%) and less than 65 years (76%). PAH was idiopathic in 72% and WHO functional class II or III in 99%. The baseline mean (SD) 6-minute walk distance was 337 (109) meters and 65% subjects walked <380 meters. Most subjects (83%) were PAH-treatment naïve.

Table 4. Demographic and Baseline Characteristics (ITT population)

	Sildenafil 5 mg (N=129)	Sildenafil 20 mg (N=128)	Sildenafil 80 mg (N=128)
Sex, n (%)			
M	32 (24.8%)	26 (20.3%)	30 (23.4%)
F	97 (75.2%)	102 (79.7%)	98 (76.6%)
Age, years			
Mean (SD)	51.4 (15.0)	51.2 (15.8)	52.1 (14.7)
Median (min, max)	55.0 (19.0, 74.0)	54.0 (19.0, 75.0)	55.0 (23.0, 74.0)
Age groups (years), n (%)			
18-44	42 (32.6%)	42 (32.8%)	37 (28.9%)
45-64	56 (43.4%)	56 (43.8%)	58 (45.3%)
>=65	31 (24.0%)	30 (23.4%)	33 (25.8%)
Race, n (%)			
WHITE	104 (80.6%)	113 (88.3%)	108 (84.4%)
ASIAN	23 (17.8%)	14 (10.9%)	19 (14.8%)
HISPANIC	2 (1.6%)	1 (0.8%)	1 (0.8%)
Ethnicity, n(%)			
HISPANIC OR LATINO	5 (3.9%)	4 (3.1%)	3 (2.3%)
NOT HISPANIC OR LATINO	124 (96.1%)	124 (96.9%)	125 (97.7%)
Cohort			
PAH-treatment naive, & PAH etiology as idiopathic	79 (61.2%)	79 (61.7%)	78 (60.9%)

	Sildenafil 5 mg (N=129)	Sildenafil 20 mg (N=128)	Sildenafil 80 mg (N=128)
PAH-treatment naive, & PAH etiology as CTD/surgical repair	30 (23.3%)	30 (23.4%)	30 (23.4%)
on PAH treatment, & PAH etiology as idiopathic	14 (10.9%)	13 (10.2%)	13 (10.2%)
on PAH treatment, & PAH etiology as CTD/surgical repair	6 (4.7%)	6 (4.7%)	7 (5.5%)
Weight, kg			
Mean (SD)	76.1 (22.7)	74.9 (20.4)	73.2 (18.9)
Median (min, max)	73.4 (32.6, 148.0)	70.1 (41.0, 135.0)	70.0 (35.2, 146.0)
Height, cm			
Mean (SD)	164.7 (9.1)	164.0 (8.6)	164.1 (9.5)
Median (min, max)	165.0 (140.0, 192.0)	164.0 (143.0, 190.0)	164.0 (140.0, 187.0)
BMI, kg/m2			
Mean (SD)	28.0 (7.8)	27.7 (7.0)	27.1 (6.1)
Median (min, max)	26.0 (13.9, 49.7)	26.3 (17.3, 47.3)	26.3 (16.1, 46.2)
Country of participation, n(%)			
UKR Ukraine	26 (20.2%)	18 (14.1%)	24 (18.8%)
RUS Russia	13 (10.1%)	22 (17.2%)	14 (10.9%)
CZE Czech Republic	9 (7.0%)	16 (12.5%)	12 (9.4%)
DEU Germany	11 (8.5%)	11 (8.6%)	12 (9.4%)
ROU Romania	10 (7.8%)	8 (6.2%)	11 (8.6%)
THA Thailand	9 (7.0%)	8 (6.2%)	11 (8.6%)
LVA Latvia	6 (4.7%)	6 (4.7%)	8 (6.2%)
All other countries	45 (34.9%)	39 (30.5%)	36 (28.1%)
Source: Reviewer's results			

Reviewer's comment: The study was conducted in 23 countries in Europe, Asia, Australia and South Africa and North America—US sites accounted for 2.6% of randomized subjects. No Black subjects were randomized and Hispanic or Latino subjects were 3%. The study does not reflect the racial or ethnic differences of patients with PAH in the US. In the PAH Biobank of 1837 patients, 79% were White, 11% were Black and 10% were Hispanic.[9]

[9] Al-Naamani N, Paulus JK, Roberts KE, et al. Racial and ethnic differences in pulmonary arterial hypertension. Pulm Circ. 2017;7(4):793-796. doi:10.1177/2045893217732213

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All 3 treatment groups were well balanced with respect to primary diagnosis, baseline disease severity and etiology of PAH (Table 5).

Table 5. Baseline Disease Characteristics (ITT population)

	Sildenafil 5 mg N=129 n(%)	Sildenafil 20 mg N=128 n(%)	Sildenafil 80 mg N=128 n(%)
Etiology, n (%)			
IDIOPATHIC	93 (72.1%)	92 (71.9%)	91 (71.1%)
SECONDARY TO CONNECTIVE TISSUE DISEASE	32 (24.8%)	27 (21.1%)	25 (19.5%)
SECONDARY TO SURGICAL REPAIR	4 (3.1%)	9 (7.0%)	12 (9.4%)
CLASS II	50 (38.8%)	41 (32.0%)	57 (44.5%)
CLASS III	68 (52.7%)	80 (62.5%)	61 (47.7%)
CLASS IV	3 (2.3%)	1 (0.8%)	1 (0.8%)
Missing	8 (6.2%)	6 (4.7%)	9 (7.0%)
Treatment History, n (%)			
Treated	20 (15.5%)	19 (14.8%)	25 (19.5%)
Naïve	109 (84.5%)	109 (85.2%)	103 (80.5%)
6MWD, meters			
Mean (SD)	330.0 (107.8)	331.4 (106.8)	349.2 (111.4)
Median (min, max)	342.0 (64.5, 588.0)	331.8 (54.5, 631.0)	352.0 (100.0, 631.5)
Missing	1.0 (0.8%)		1.0 (0.8%)
6MWD groups, n (%)			
< 380 meters	88 (68.2%)	85 (66.4%)	76 (59.4%)
>=380 meters	40 (31.0%)	43 (33.6%)	51 (39.8%)
Missing	1 (0.8%)		1 (0.8%)
Predicted Total Lung Capacity, %			
Mean (SD)	94.8 (22.7)	90.7 (19.6)	93.1 (20.0)
Median (min, max)	92.0 (63.0, 204.0)	89.9 (3.3, 142.0)	94.0 (0.0, 139.5)
Missing	57.0 (44.2%)	59.0 (46.1%)	59.0 (46.1%)
Predicted FEV1, %			
Mean (SD)	85.5 (18.9)	85.8 (17.9)	87.2 (17.7)
Median (min, max)	84.0 (39.0, 158.0)	84.0 (2.8, 118.0)	83.5 (58.0, 134.0)
Missing	46.0 (35.7%)	45.0 (35.2%)	38.0 (29.7%)

[Source: Reviewer's results]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Noncompliance (defined as subject takes less than 80 percent of study medication or more than 120 percent of treatment while on active study treatment) as assessment pill counts ranged

from 9% (20 mg) to 20% (80 mg). Sildenafil concentrations were not obtained to assess compliance.

The percentages of subjects who took prohibited concomitant medications or who did not take permitted ones as specified were low and similar across treatment groups (5–6%). Prohibited medications included bosentan, riociguat, another PDE-5 inhibitor, CYP3A inducer/inhibitor, or nitrates or nitric oxide.

Efficacy Results – Primary Endpoint of Overall Survival

A Cox proportional hazard model with stratification factors of previous PAH-treatment and etiology was used to estimate the pair-wise HRs for sildenafil 80 mg TID relative to sildenafil 5 mg TID, sildenafil 80 mg TID relative to sildenafil 20 mg TID, and sildenafil 20 mg TID relative to the sildenafil 5 mg TID.

Table 6 summarizes the analysis of mortality HRs regarding overall survival for the stratified Cox model. The primary comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID yields a HR (99.7% CI) = 0.51 (0.22, 1.21). Since the upper limit of the 99.7% CI for the HR is less than the pre-specified non-inferiority margin of 2, non-inferiority of sildenafil 80 mg vs. sildenafil 5 mg regarding time to death (mortality) was shown. Thus, the primary objective of the study was met.

Table 6. Hazard Ratios for Overall Survival - ITT Population

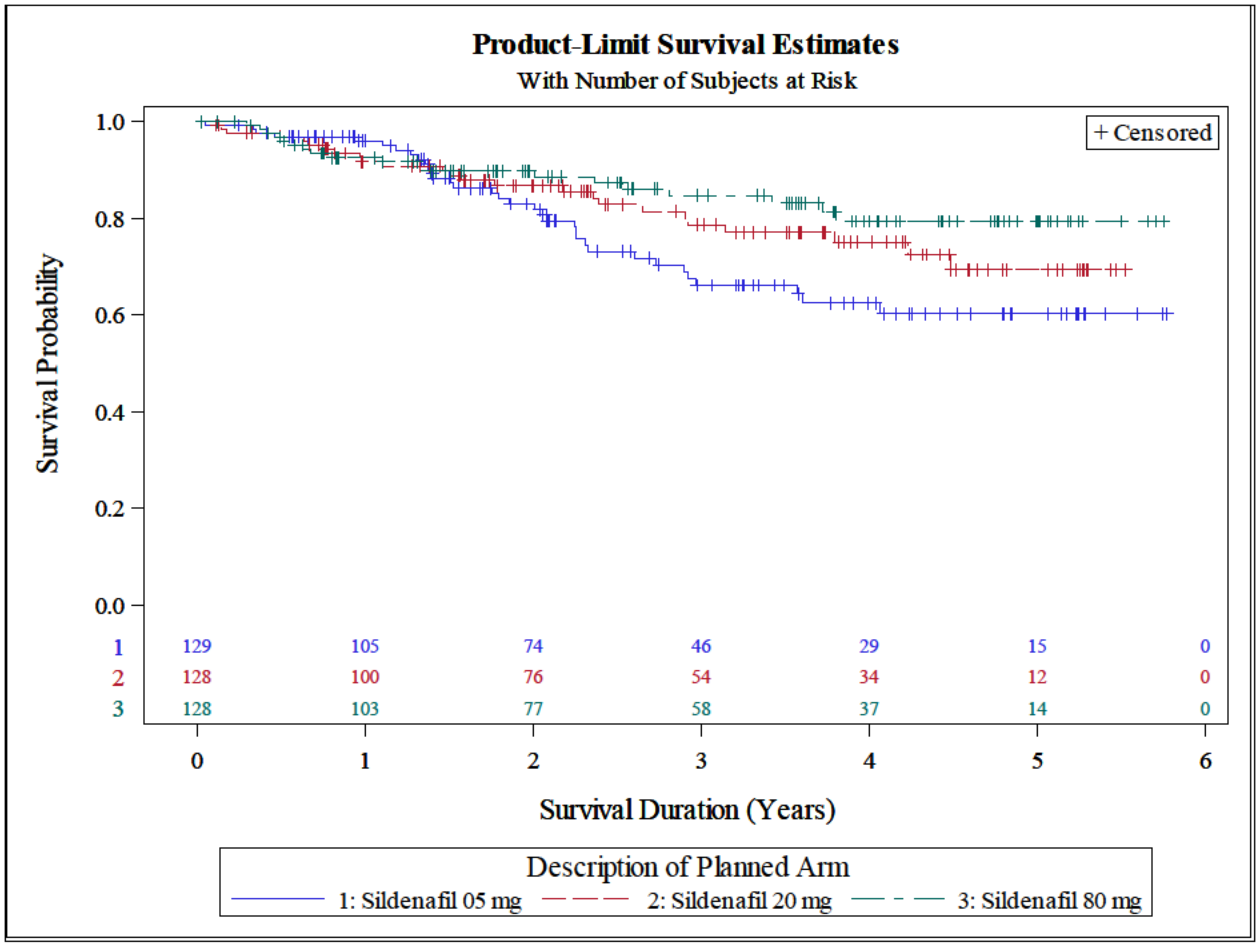
	Sildenafil 5 mg N=129	Sildenafil 20 mg N=128	Sildenafil 80 mg N=128
Subject-years of follow-up	329.8	340.5	356.7
Deaths (%)	34 (26.4)	24 (19.5)	19 (14.8)
On treatment deaths	22 (17.1)	13 (10.2)	15 (11.7)
Off treatment deaths	12 (9.3)	12 (9.4)	4 (3.1)
HR vs. 5mg		0.68	0.51
99.7% CI (P-value)		0.31, 1.49 (0.142)	0.22, 1.21 (0.021)
HR vs. 20mg			0.74
99.7% CI (P-value)			0.30, 1.84 (0.333)

[Treatment comparisons for 80 mg vs. 20 mg, and 20 mg vs. 5 mg are considered secondary analyses with no p-value adjustment specified. Source: Reviewer's results]

A Kaplan-Meier plot of overall survival for the ITT Population is provided in Figure 2. The Kaplan-Meier estimate for survival after one year was numerically higher for sildenafil 5 mg TID compared with sildenafil 20 mg TID and sildenafil 80 mg TID. Throughout Year 2 to Year 6, the

Kaplan-Meier estimate for survival for sildenafil 80 mg TID was numerically higher compared to sildenafil 20 mg TID and sildenafil 5 mg TID.

Figure 2. Kaplan-Meier Plot of Survival by Treatment Group - ITT Population



[Source: Reviewer's results]

Table 7 summarizes the analysis of mortality HRs regarding overall survival for the stratified Cox model regarding PAH treatment at entry, etiology of PAH, Sex, Race, and Age groups. For subjects with previous PAH treatment, non-inferiority was not shown for sildenafil 80 mg TID vs. sildenafil 5 mg TID due to the small sample size but the HR was 0.29. For subjects with treatment-naïve PAH, non-inferiority was demonstrated for sildenafil 80 mg TID vs. sildenafil 5 mg TID. Non-inferiorities were demonstrated for sildenafil 80 mg TID vs. sildenafil 5 mg TID for both etiology strata. Furthermore, non-inferiorities were not demonstrated for sildenafil 80 mg TID vs. sildenafil 5 mg TID in some subgroups of Sex, Age and Race groups due to small sample sizes. However, the HRs are all numerically in favor of sildenafil 80 mg TID.

Table 7. Hazard Ratios for Overall Survival by Subgroups

Subgroups	Sildenafil 5 mg	Sildenafil 80 mg	HR (99.7% CI)
Previous PAH (n/N)			
Treated	5/20	2/25	0.29 (0.02, 3.74)
Naïve	29/109	17/103	0.55 (0.22, 1.38)
Etiology of PAH			
Idiopathic	23/93	14/91	0.59 (0.21, 1.63)
Secondary to CTD/surgical repair	11/36	5/37	0.37 (0.07, 1.85)
Sex (n/N)			
Male	12/32	6/30	0.54 (0.12, 2.51)
Female	22/97	13/98	0.50 (0.17, 1.45)
Race (n/N)			
White	25/104	14/108	0.52 (0.19, 1.42)
Asian	9/23	5/19	0.50 (0.09, 2.78)
Other	0/2	0/1	N/A
Age Groups (n/N)			
18-44	8/42	5/37	0.62 (0.11, 3.46)
45-64	16/56	7/58	0.36 (0.09, 1.47)
>=65	10/31	7/33	0.62 (0.14, 2.81)

[Source: Reviewer's results]

Data Quality and Integrity

Four subjects had randomization stratification errors: 2 had PAH treatment at entry but randomized as Naïve and 2 subjects were treatment Naïve at entry but randomized as Treated (see CSR Table 16.2.5.1.2). These 4 subjects were all in Sildenafil 5 mg TID arm and only 1 of them had died while on treatment, which had no impact to conclusions of the subgroup analyses of Table 7.

Efficacy Results – Secondary endpoints

Time to First Event of Clinical Worsening

The results for time to first event of clinical worsening for the comparison of sildenafil 80 mg

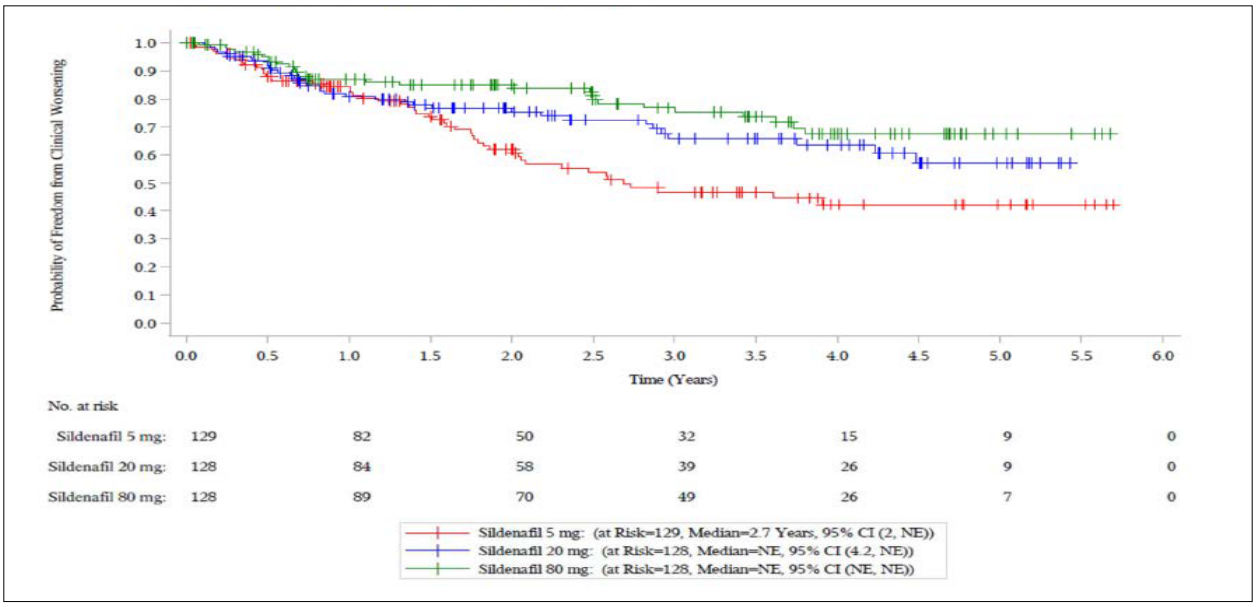
TID vs. sildenafil 5 mg TID yield a HR (99.7% CI) = 0.44 (0.22, 0.89) with p-value <0.001, see Table 8. Figure 3 shows that throughout Year 1 to Year 5, the Kaplan-Meier estimate (95% CI) for sildenafil 80 mg TID was numerically higher compared to sildenafil 20 mg TID and sildenafil 5 mg TID.

Table 8. Hazard Ratios for Time to First Event of Clinical Worsening

	Sildenafil 5 mg N=129	Sildenafil 20 mg N=128	Sildenafil 80 mg N=128
Clinical Worsening n (%) Disease Progression Hosp for PAH Death	52 (40.3) 8 (6.2) 28 (22.2) 16 (12.4)	36 (28.1) 2 (1.6) 23 (18.0) 11 (8.6)	28 (21.9) 6 (4.7) 11 (8.6) 11 (8.6)
HR vs. 5mg 99.7% CI P-val		0.63 0.33 1.21 0.035	0.44 0.22, 0.89 0.0005
HR vs. 20mg 99.7% CI P-val			0.71 0.33, 1.52 0.195

[Treatment comparison was conducted using Cox proportional hazard regression model stratified by PAH treatment at entry of the study (PAH-treatment naïve vs. on PAH treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). There was no p-value adjustment for secondary endpoints analyses. Source: Reviewer's results.]

Figure 3. Kaplan-Meier Plot of Time to First Event of Clinical Worsening by Treatment Group



[Source: reviewer's results]

Table 9 summarizes the analysis of time to first event of clinical worsening HRs regarding PAH treatment at entry, etiology of PAH, Sex, Age group and Race. For subjects with previously treated PAH, the results for time to first event of clinical worsening for the comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID yielded a HR (99.7% CI) = 0.28 (0.05, 1.69). For subjects with treatment-naive PAH, the results for time to first event of clinical worsening for the comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID yield a HR (99.7% CI) = 0.48 (0.23, 1.03). For subjects with idiopathic PAH, the results for time to first event of clinical worsening for the comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID yielded a HR (99.7% CI) = 0.46 (0.20, 1.07). For subjects with PAH secondary to CTD/surgical repair, the results for time to first event of clinical worsening for the comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID yield a HR (99.7% CI) = 0.39 (0.11, 1.37). Furthermore, the results for time to first event of clinical worsening numerically favored sildenafil 80 mg TID vs. sildenafil 5 mg TID in all subgroups of Sex, Age and Race groups.

Table 9. Hazard Ratios for Clinical Worsening by Subgroups

Subgroups	Sildenafil 5 mg	Sildenafil 80 mg	HR (99.7% CI)
Previous PAH (n/N)			
Treated	9/20	4/25	0.28 (0.05, 1.69)
Naïve	43/109	24/103	0.48 (0.23, 1.03)

Subgroups	Sildenafil 5 mg	Sildenafil 80 mg	HR (99.7% CI)
Etiology of PAH (n/N)			
Idiopathic	36/93	19/91	0.46 (0.20, 1.07)
Secondary to CTD/surgical repair	16/36	9/37	0.39 (0.11, 1.37)
Sex (n/N)			
Male	18/32	8/30	0.34 (0.09, 1.26)
Female	34/97	20/98	0.47 (0.20, 1.11)
Race (n/N)			
White	41/104	21/108	0.43 (0.19, 0.96)
Asian	11/23	7/19	0.40 (0.08, 1.92)
Other	0/2	0/1	N/A
Age Groups (n/N)			
18-44	12/42	7/37	0.49 (0.12, 2.05)
45-64	27/56	11/58	0.29 (0.10, 0.87)
>=65	13/31	10/33	0.82 (0.22, 2.98)

[Source: Reviewer's results]

6MWD at Months 6 and 12

Using MMRM for treatment comparison of 6MWD change from baseline at Month 6 for the ITT Population, least square (LS) means for sildenafil 20 mg TID and sildenafil 80 mg TID were 27.7 and 31.5 meters, respectively, compared to 12.1 meters for sildenafil 5 mg TID. The LS means difference of 19.4 meters for sildenafil 80 mg TID vs. sildenafil 5 mg TID with a nominal p-value of 0.017, which also did not reach the pre-specified 2-sided significance level of 0.003 (Table 10).

Similarly, using MMRM for treatment comparison of 6MWD change from baseline at Month 12 for the ITT Population, LS means for sildenafil 20 mg TID and sildenafil 80 mg TID were 34.4 and 32.2 meters, respectively, compared to 11.3 meters for sildenafil 5 mg TID. Both the LS means difference of 20.9 meters for sildenafil 80 mg TID also did not reach statistically significant difference vs. sildenafil 5 mg TID with nominal p-values of 0.041 (Table 10).

Table 10. Treatment Comparison of 6-Minute Walk Distance Change from Baseline at Month 6 and Month 12 Using MMRM

	Sildenafil 5 mg N=129	Sildenafil 20 mg N=128	Sildenafil 80 mg N=128
Baseline (SD)	330.0 (107.8)	331.4 (106.8)	349.2 (111.4)
Change from baseline at M6 (SE)	12.1 (6.7)	27.7 (6.6)	31.5 (6.4)
vs. 5mg			
LS Means Difference		15.6	19.4
95% CI		(-0.14, 31.4)	(3.52, 35.3)
p-value		0.052	0.017
vs. 20mg			
LS Means Difference			3.8
95% CI			(-11.9, 19.5)
p-value			0.635
Change from baseline at M12 (SE)	11.3 (8.2)	34.4 (8.1)	32.2 (8.0)
vs. 5mg			
LS Means Difference		23.1	20.9
95% CI		(3.25, 43.0)	(0.91, 40.8)
p-value		0.023	0.041
vs. 20mg			
LS Means Difference			-2.2
95% CI			(-22.0, 17.5)
p-value			0.823

[Source: Reviewer's results]

6.2 Study A1481131 (STARTS-1) and Study A1481156 (STARTS-2)

6.2.1 Study Design

Overview and Objectives

Studies STARTS-1 and STARTS-2 were previously reviewed by Drs. Gordon (clinical), Lawrence (statistics), and Brar (Clinical Pharmacology) under NDA 203109. Their reviews are in DARRTS. A summary of findings from their reviews are presented to support the pediatric indication, benefit-risk assessment and labeling.

Trial Design

STARTS-1 was a randomized, double-blind, multi-center, placebo controlled parallel group, dose ranging study. The study included subjects, aged 1 to 17 years with body weight ≥8 kg, and with

primary PAH, or PAH secondary to congenital heart disease including those who had a surgical repair ≥6 months prior to screening, or collagen vascular disease.

Subjects received 1 of 3 sildenafil doses (low, medium or high), or placebo. Actual doses administered were dependent on body weight (Table 11). Subjects were stratified according to weight and developmental ability to perform the cardiopulmonary exercise test (CPET). With the exception of the subjects weighing ≤20 kg, subjects were randomized 1:1:1:1 to sildenafil low, medium and high doses, and placebo, respectively. Subjects weighing from 8 to 20 kg were randomized 1:2:1 to sildenafil medium and high doses, and placebo, respectively.

Table 11. Sildenafil doses administered three times daily (TID)

Body Weight	Sildenafil Dose mg TID[1]		
	Low	Medium	High
≥8–20 kg	Not treated[2]	10	20
>20–45 kg	10	20	40
>45 kg	10	40	80

[1]Pediatric doses were selected based on body weight such that these approximate target plasma concentrations would achieve maximum steady state concentration ($C_{max,ss}$) of 47, 140 and 373 ng/mL for the low, medium and high doses, respectively. These target concentrations are expected to be similar to sildenafil concentrations that produced approximately 53%, 77%, and 90% inhibition of PDE-5 activity in the in vitro assay.

[2]Tablet strength for lowest body weight was not available (lowest tablet strength was 10 mg)

STARTS-2 was the long-term extension study. Subjects who completed STARTS-1 study were eligible to enter the extension study A14811565 (STARTS-2). Those subjects who received placebo in STARTS-1 were stratified by weight and randomized to receive sildenafil as per 1 of the active treatment groups in STARTS-2. The extension study was initially a double-blind study; the blind was maintained until the final subjects completed STARTS-1 and the database locked, to protect against bias in the STARTS-1 study.

Key Inclusion and Exclusion Criteria

The study included subjects, aged from 1 to 17 years (subject to country specific protocols), weighing ≥8 kg and had symptomatic PAH due to 1 of the following conditions:

- Primary PAH (idiopathic or hereditary PAH);
- PAH in the presence of a small or hemodynamically insignificant congenital systemic to pulmonary shunt lesion that in the opinion of the investigator was not the cause of PH;
- PAH associated with collagen vascular disease (e.g., scleroderma);

- PAH associated with congenital systemic-to-pulmonary shunts with a baseline resting room air oxygen saturation ≥88%. If the defect was repaired, it should have been repaired ≥6 months prior to screening (repairs could be either surgical or via interventional cardiac catheterization (e.g., atrial septal defect closure device or coil of patent ductus arteriosus));
- PAH associated with d-transposition of the great arteries repaired within the first 30 days of life;
- PAH in subjects who had undergone surgical repair of other congenital heart lesions ≥6 months prior to screening and did not have clinically significant residual left-sided heart disease consistent with exclusion criteria.

Subjects were excluded from the study if they had PH secondary to other diseases, left-sided heart disease and other similar heart-related diseases, or had treatment with off-label sildenafil, an endothelin-A receptor antagonists or prostacyclin/prostacyclin analogue within 30 days prior to randomization, or who were taking medications such as parenteral inotropic medication, parenteral vasodilators within 3 months prior to screening, alpha-blockers or cytochrome P450 (CYP) 3A4 inhibitors.

Study Endpoints

Primary: Maximal VO2 ml/kg/min obtained by CPET

Secondary:

- Key secondary: PVRI
- Hemodynamic parameters: cardiac index, mPAP, PVR and systemic vascular resistance (SVR).
- WHO functional class

Reviewer's comment: Measuring the primary endpoint, maximal VO2, in the entire pediatric age range was not feasible. An Advisory Committee meeting was held on July 29, 2010 to discuss the usefulness of changes in PVRI as a bridging biomarker for pediatrics. The committee concluded that, for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population. FDA modified the sildenafil pediatric WR to reflect this interest in PVRI changes for pediatric extrapolation.

6.2.2 Study Results

A total of 234 subjects with PAH aged 1 to 17 years were treated and 228 subjects completed the study, of which 220 subjects entered the extension study A14811565 (STARTS-2). Of those subjects who started study treatment, 6 subjects discontinued: 2 subjects each in the sildenafil low, sildenafil high and placebo treatment groups.

Overall, subjects were predominantly female (62%). PAH was idiopathic or heritable in 33% and associated with congenital heart defect in 67%; mean time from diagnosis was 1.7 (range, 0–12) years for idiopathic PAH and 6.0 (range, 0–17) years for congenital heart defect-based PAH, respectively. Disease was World Health Organization (WHO) functional class I or II in 83% of patients. Mean (±SD) PVRI was 15±10 and 20±15 Wood units/m^2 for placebo-treated and sildenafil-treated subjects, respectively.

> *Reviewer's comments: The distribution of subjects across treatment groups was not balanced because no subject with weight <20 kg was randomized to the sildenafil low treatment group, and the randomization allocation to sildenafil medium, high and placebo groups was 1:2:1 in this weight group. The placebo cohort had lower percentage of subjects with baseline WHO FC III/IV (10%); PVRi >15.1 (37%); mPAP ≥62 (40%) and Cardiac index <3.2 (37%).*

Patients were naïve for specific PAH therapy and the use of prostacyclin; prostacyclin analogues and endothelin receptor antagonists were not permitted in the study. Also, arginine supplementation, nitrates, alpha-blockers and potent CYP450 3A4 inhibitors were not permitted.

Efficacy Endpoint: Peak VO_2

CPET was performed in 115 developmentally able subjects, of which 106 were evaluable. None of the 63 patients aged <7 years were able to perform the exercise test. Among 171 subjects aged ≥7 years, 56 subjects were developmentally unable to reliably exercise. Reasons provided were Down syndrome (n=31); inability to reach bicycle pedals; and various other reasons, including unwillingness to wear mask, dyspnea, and low physical activity.

The primary efficacy endpoint was the percent change in peak VO2 (normalized to body weight) at trough plasma levels from baseline to Week 16 using last observation carried forward (LOCF) for missing data imputation (Table 12). The baseline value was taken as the average of the screening and baseline readings. The study failed to show a significant effect of sildenafil on the primary endpoint in the subset of children who were developmentally able to exercise (n=115). The combined doses (low, medium and high) produced a statistically insignificant 7.7% increase in the peak VO2 treatment effect (p=0.056). The low dose had a similar mean percentage change from baseline to the placebo group (difference of 4%), while both the medium and high dose groups displayed greater increases compared to placebo (11% and 8%, respectively).

With few subjects excluded from the primary analyses due to missing data, the analyses when using different approaches for handling missing values gave similar results to the primary analysis.

Table 12. Peak VO2 at Week 16 (LOCF, ITT population in Study A1481131)

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects[a]	24	26	27	77	29
Mean (SD) VO_2, mL/kg/minute					
Baseline[b]	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Week 16	18.40 (5.61)	20.39 (6.16)	19.00 (3.59)	19.28 (5.21)	20.01 (4.44)
Change from baseline	1.03 (3.41)	2.36 (3.36)	1.57 (2.56)	1.67 (3.13)	-0.01 (3.34)
Percentage change from baseline	6.44 (20.16)	13.40 (19.50)	10.58 (15.51)	10.24 (18.39)	0.53 (15.91)
Mean difference versus placebo (SE)[c]	3.81 (5.00)	11.33 (4.84)	7.98 (4.85)	7.71 (3.98)	NA
95% Confidence interval[c]	-6.11, 13.73	1.72, 20.94	-1.64, 17.60	-0.19, 15.60	NA
P-value[c]	NA	NA	NA	0.056	NA

Source: Tables 5.2.1.1 and 5.2.2
VO_2=volume of oxygen consumed; LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; NA=not applicable
[a] ITT subset of developmentally able subjects
[b] Baseline was the average of all assessments on or before the first day of study treatment
[c] Analyses were performed using analysis of covariance with etiology, weight and baseline peak VO_2 as the covariates

[Source: Applicant's table, confirmed by FDA]

In the subset of children who could undergo CPET, there was no improvements in peak V02 in STARTS-2 at 1 year after starting sildenafil treatment. The mean percent increase of peak VO2 values were 9.9, 6.0, and 2.5 for sildenafil low, medium and high dose, respectively. The mean percent increase for the sildenafil low dose was statistically significant, but the results from sildenafil medium and high doses were not. Hemodynamics were not collected in STARTS-2.

Key Hemodynamic Endpoint: PVRI

Decreases from baseline in mean PVRI were observed for the sildenafil combined dose groups (Table 13). The sildenafil combined group showed a decrease compared to placebo in PVRI of -4.1 Wood units/m^2 (95% CI: -8.0 to -0.2).

Table 13. PVRI at Week 16 (LOCF, ITT population in Study A1481131)

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects	36	49	67	152	50
Mean (SD) PVRI, Wood units/m^2					
Baseline[a]	23.5 (15.2)	19.0 (13.8)	20.9 (19.0)	20.9 (16.6)	16.1 (12.0)
Week 16	23.6 (16.0)	16.0 (11.0)	15.8 (13.5)	17.7 (13.7)	17.7 (13.8)
Change from baseline	0.1 (10.9)	-2.9 (11.5)	-5.1 (14.7)	-3.2 (13.0)	1.6 (9.2)
Mean difference versus placebo (SE)[b]	-0.6 (2.7)	-4.5 (2.4)	-7.2 (2.3)	-4.1 (2.0)	NA
95% Confidence interval[b]	-5.9, 4.7	-9.3, 0.3	-11.7, -2.7	-8.0, -0.2	NA
P-value[b]	NA	NA	NA	0.041	NA

Source: Tables 5.4.1 and 5.4.2.1
PVRI=pulmonary vascular resistance index; LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; SD=standard deviation; NA=not applicable
[a] Baseline was the last PVRI assessment from 21 days before study treatment to the first day of study treatment
[b] Analyses were performed using analysis of covariance with etiology, weight and ability to perform the cardiopulmonary exercise test as the covariates

[Source: Applicant's Table T17 in CSR, confirmed by FDA]

Additional Analyses Conducted on the Individual Trial

Although STARTS-1 failed to show a significant effect of sildenafil on the pre-specified primary endpoint in pool dose groups (low, medium and high), post-hoc analyses of the peak VO_2 and PVRI data provided evidence for efficacy with the pooled medium and high doses. The post-hoc analyses were based on pediatric extrapolation concepts which aim to leverage the adult efficacy data to maximize the understanding of key efficacy endpoints collected in pediatrics.[10] The CRDAC considered that PAH (WHO Group 1) in children to be sufficiently similar to the disease in adults to use pediatric extrapolation.[11]

Efficacy Issue 1. Low dose group had unexpectedly lower sildenafil concentrations

The Applicant used pharmacokinetic-pharmacodynamic modeling to determine the body-weight based doses which gave approximate target $C_{max,ss}$ of 47, 140 and 373 ng/mL for the low, medium and high doses, respectively. These target concentrations were expected to be similar

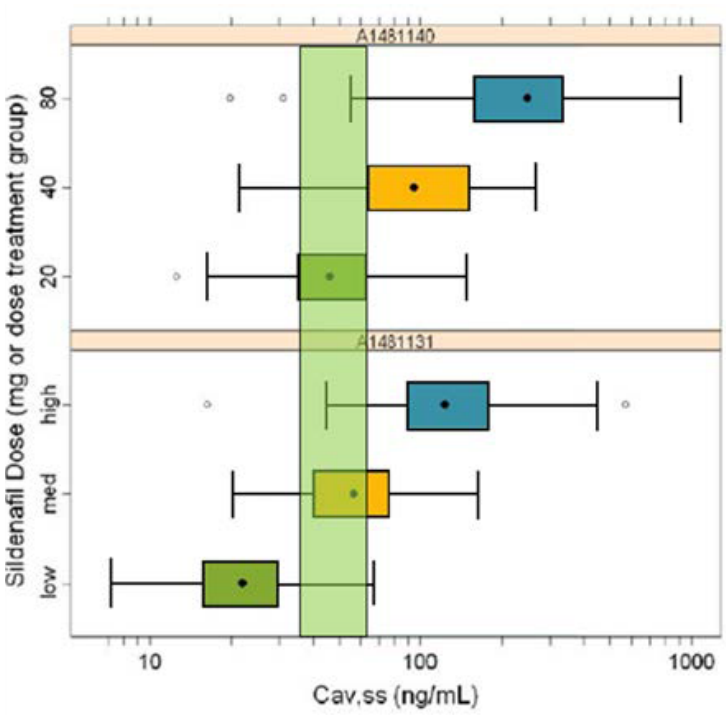
[10] ICH E11a Pediatric Extrapolation: https://database.ich.org/sites/default/files/ICH_E11A_Document_Step2_Guideline_2022_0404_0.pdf

[11] Cardiovascular and Renal Drug Advisory Committee Meeting: http://wayback.archive-it.org/7993/20170112101610/http://www.fda.gov/AdvisoryCommittees/Calendar/ucm217266.htm

to sildenafil concentrations that produced approximately 53%, 77% and 90% inhibition of PDE-5 activity in the in vitro assay.

Analysis of the concentration data from STARTS-1, however, showed the majority of the subjects in the low dose had steady-state concentrations below the IC50 for PDE-5 inhibition (47 ng/mL). Furthermore, the medium dose provided similar steady-state concentrations to those in adults taking the labeled dose, 20 mg TID (Figure 4).

Figure 4. Boxplot of predicted average steady state sildenafil concentrations for adults (Study A1481140: 20, 40 and 80 mg TID) and pediatrics >45 kg, >20 to <45kg and 8 to 20 kg weight groups that were randomized to a high (blue), medium (yellow) or low (green) dose.



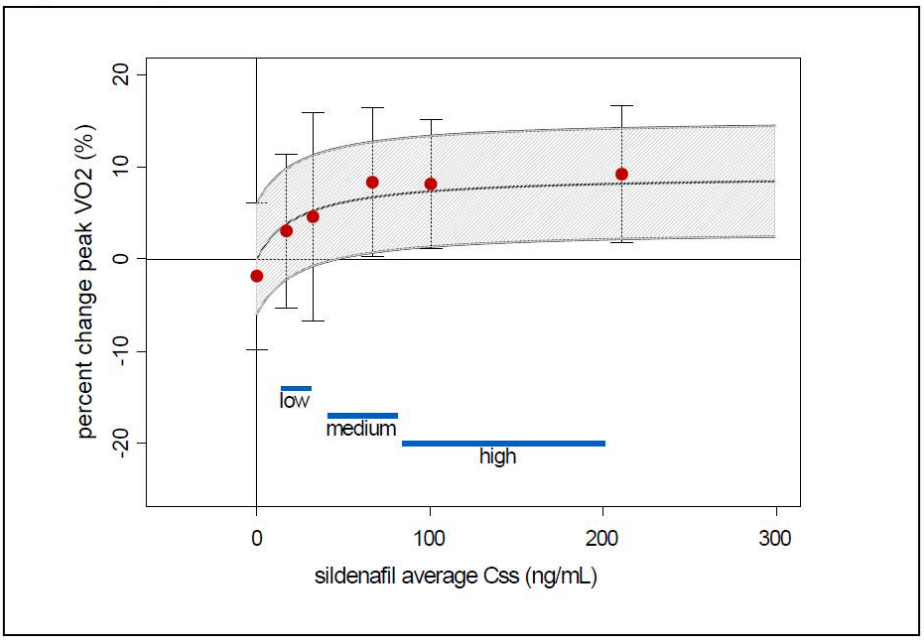
[Black dot within each box represents the medium steady-state sildenafil concentrations within each dose group. Green shaded bar represents the interquartile range of the steady state concentrations for the approved adult dose of 20 mg TID. Clinical Pharmacology Review, 2012]

Issue 2. Improvements in peak VO2 and PVRI with the medium and high dose groups

When the low-dose group was excluded from analysis, the placebo-corrected increase in peak VO_2 for the combined medium- and high-doses was 9.7% (95% CI, 1.3% to 18%).

The increase in peak VO_2 observation with the medium and high doses is supported by exposure-response analysis (Figure 5). A near maximum effect of 9% change in peak VO_2 was achieved at concentrations corresponding to medium and high doses.

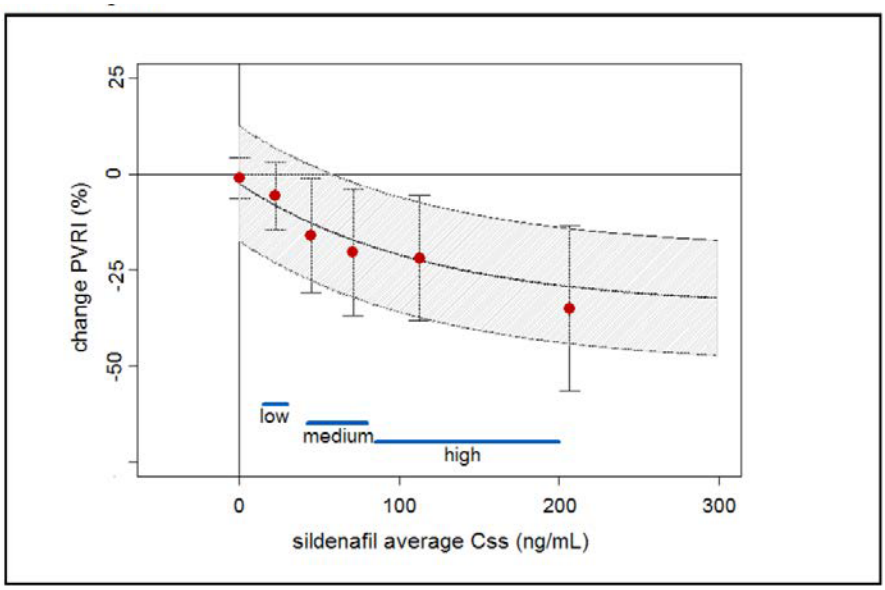
Figure 5. Exposure-response for changes in VO_2 peak at 16 weeks from baseline (LOCF, ITT population in Study A1481131, mean ± 95% CI)



[Emax exposure-response relationship for percent change in peak VO_2 at 16 weeks and predicted average sildenafil steady state concentration (Css). The solid symbols and bars represent the mean and 95% confidence interval of peak VO_2 increase from baseline for each concentration quantile. The interquartile ranges for the low, medium and high doses are denoted by the horizontal lines. The solid line represents the mean prediction from the Emax relationship and its corresponding 95% confidence interval (shaded region). Clinical Pharmacology Review, 2012]

Consistent with peak VO_2, an Emax exposure-response relationship was observed for percent change in PVRI at 16 weeks and predicted average sildenafil steady state concentration (Figure 6). The maximum effect on PVRI of -31% was achieved at concentrations corresponding to the medium and high doses.

Figure 6. Exposure-response for changes in PVRI at 16 weeks from baseline (LOCF, ITT population in Study A1481131, mean ± 95% CI)



[For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of PVRI decrease from baseline for each concentration quantile. The interquartile ranges for the low, medium and high doses are denoted by the horizontal lines. The solid line represents the mean prediction from the Emax relationship and its corresponding 95% confidence interval (shaded region). Clinical Pharmacology Review, 2012]

The pooled medium and high doses in pediatrics gave similar treatment effect on both exercise capacity and PVRI as adults taking sildenafil 20 mg TID in study A1481140[12].

[12] Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension [published correction appears in N Engl J Med. 2006 Jun 1;354(22):2400-1]. N Engl J Med. 2005;353(20):2148-2157. doi:10.1056/NEJMoa050010

Table 14. Comparison of Exercise Capacity and Pulmonary Vascular Resistance Index Effect in pediatric (medium and high doses pooled) and adult (20 mg TID) populations

	Placebo corrected % change from baseline	95% CI
Exercise capacity*		
Adults (A1481140)	13.10	(5.2, 21.3)
Pediatrics (A1481131)	9.65	(1.3, 18.0)
PVRI		
Adults (A1481140)	21.20	(10.5, 29.9)
Pediatrics (A1481131)	22.80	(10.1, 34.1)

*[*Exercise capacity was measured by 6-minute walk distance in adults and VO_2 using CPET in pediatrics. Clinical Pharmacology Review, 2012]*

7 Integrated Review of Effectiveness

7.1 Effectiveness in the Pediatric PAH Population

Although study A1481131 (STARTS-1) failed to meet its primary efficacy endpoint, percent change in peak VO2 (normalized to body weight) from baseline to Week 16 in combined doses (low, medium and high), the clinical review team concludes that the effectiveness of sildenafil in the treatment of PAH in pediatric subjects has been demonstrated based on the exercise, hemodynamics and exposure-response data collected in STARTS-1 for the medium and high doses.

Both the pediatric and adult populations had similar treatment effect on PVRI [22.8% reduction in pediatrics in STARTS-1 vs. 21.2% reduction in adults in Study A1481140[13]]. The significant improvement in PVRI in STARTS-1 is consistent with the change in PVO2 being clinically relevant because changes in PVR correlates with changes in exercise capacity as measured by the 6-minute walk test in adults with PAH.

[13] Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension [published correction appears in N Engl J Med. 2006 Jun 1;354(22):2400-1]. N Engl J Med. 2005;353(20):2148-2157. doi:10.1056/NEJMoa050010

There was internal consistency with other efficacy endpoints in STARTS-1 at 16 weeks. Overall, the medium and high sildenafil doses were associated with improved exercise capacity, WHO functional class, hemodynamic parameters (PVRI, mPAP) and parent/physician global assessments.

In the subset of children who could undergo CPET, there was no further improvements in peak $V0_2$ in STARTS-2 at 1 year after starting sildenafil treatment. The mean percent increases of peak VO2 were 9.9, 6.0, and 2.5 for sildenafil low, medium and high dose, respectively. The mean percent increase for the sildenafil low dose was statistically significant, but the results from sildenafil medium and high doses were not. Hemodynamics were not collected in STARTS-2.

Overall, sildenafil showed a small treatment effect (improved exercise capacity, PVRI, mPAP and WHO functional class) in STARTS-1 after 16 weeks of treatment.

7.2 Effectiveness of the 5 mg TID Dose in Adult PAH

(b) (4) Study A1481244, a 12-week dose-response study investigating the use of 1 mg, 5 mg and 20 mg TID sildenafil in treating subjects with PAH that was less severe, but where chronic therapy was needed. The primary efficacy endpoint was the 6MWD. Study A1481244 demonstrated an increase in total distance walked in each treatment group during the 6MWD at Week 12 (LOCF, ITT population). The increase was clinically significant in the 5 mg and 20 mg groups (mean changes of 41 meters [95% CI: 25.16, 56.34] and 38 meters [95% CI: 23.77, 52.94], respectively), but smaller and not clinically significant in the 1 mg group.

A1481324 showed that long-term efficacy of 5mg TID was not as good as the higher doses.

- For clinical worsening, the Kaplan-Meier estimates for sildenafil 80 mg TID were numerically higher against sildenafil 20 mg TID and sildenafil 5 mg TID throughout Year 1 to Year 5.
- The results for time to first event of clinical worsening for the comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID yielded a HR (99.7% CI) = 0.44 (0.22, 0.89) with p-value <0.001.
- The results for time to first event of clinical worsening for the comparison of sildenafil 20 mg TID vs. sildenafil 5 mg TID yielded a HR (99.7% CI) = 0.63 (0.33, 1.21) with p-value 0.035.
- For 6MWD at month 6, the median change from baseline was highest for sildenafil 80 mg TID with 31.5 m compared to 12.1 m and 27.7 m for sildenafil 5 mg TID and sildenafil 20 mg TID, respectively.
- For 6MWD at month 12, the median change from baseline was highest for sildenafil 80 mg TID with 32.2 m compared to 11.3 m and 34.4 m for sildenafil 5 mg TID and sildenafil 20 mg TID, respectively.

Therefore, the positive effect of 5 mg TID dosing on 6MWD at Week 12 (b) (4) (b) (4) was not reproduced in A1481324. The 5 mg TID did not show a similar long-term improvement in 6MWD when compared to the 20 mg and 80 mg TID doses. Furthermore, this is the first study which evaluated a dose-response for clinical worsening. The 5 mg TID had increased risk for clinical worsening compared to the higher doses.

8 Review of Safety

8.1 Safety Review Approach

The adverse event profile of sildenafil is well characterized in adult subjects with PAH. The focus of the safety analysis for A1481324 was to compare the deaths, SAEs, and other important TEAEs of the 5 mg TID to the 20 mg and 80 mg TID dosing regimens. Safety analysis was conducted on the ITT populations.

For pediatrics, analysis of the deaths and serious adverse events in STARTS-2 were presented for the final dataset. Our previous review in 2012 was based on an interim dataset.

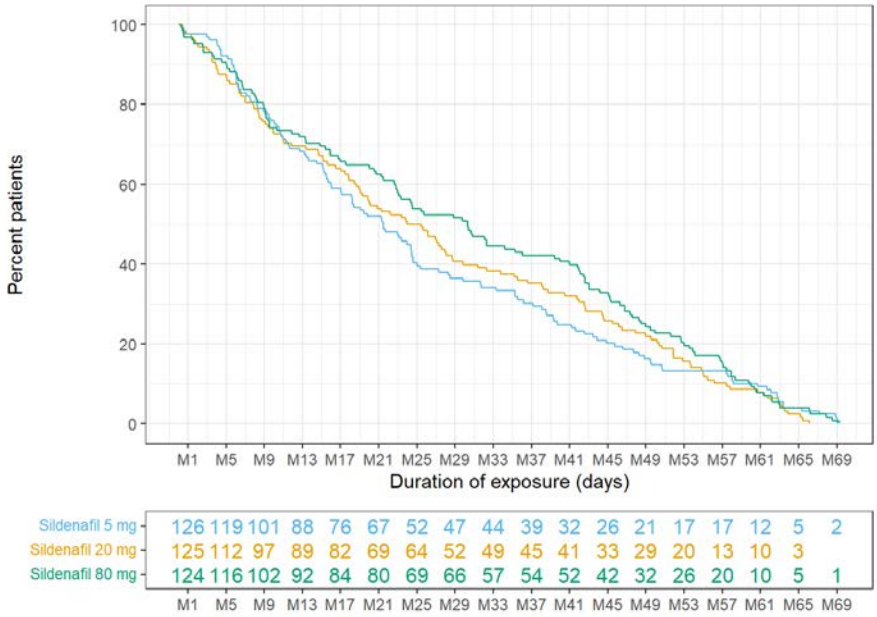
8.2 Review of the Safety Databases

8.2.1 Study A1481324

Overall Exposure

Subjects in the sildenafil 5 mg TID group had a shorter extent of exposure as shown in Figure 7 and Table 15.

Figure 7. Time Course of Treatment Exposure



[Source: Reviewer's results]

Table 15. Extent of Exposure

Exposure	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
	N=129	N=128	N=128
Duration of treatment, days			
Mean (SD)	795.2 (585.8)	842.9 (602.4)	932.9 (624.6)
Median (min, max)	645 (8.0, 2080)	741 (14.0, 1984)	910 (10.0, 2073)
Subjects treated, by duration, n(%)			
< 1 year	40 (31.0%)	39 (30.5%)	35 (27.3%)
1 - < 2 years	31 (24.0%)	25 (19.5%)	22 (17.2%)
2 - < 3 years	19 (14.7%)	18 (14.1%)	17 (13.3%)
3 - < 4 years	17 (13.2%)	17 (13.3%)	22 (17.2%)
4 - < 5 years	10 (7.8%)	19 (14.8%)	22 (17.2%)
5 - < 6 years	12 (9.3%)	10 (7.8%)	10 (7.8%)

[Source: *Reviewer's results. Abbreviations: N, number of subjects in treatment arm; n, Number of subjects with an event; CI, Confidence Interval. Cross-reference: Applicant's Table 26 in CSR.]*

Safety Results

Overview of Treatment Emergent Adverse Events

Overall, sildenafil 5 mg TID had more deaths, SAEs and severe TEAEs compared to the other dose groups (Table 16).

Table 16. Overview of TEAEs

Event	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
	N=129	N=128	N=128
	n(%)	n(%)	n(%)
Deaths	34 (26.4%)	25 (19.5%)	19 (14.8%)
SAE	66 (51.2%)	49 (38.3%)	51 (39.8%)
AE leading to permanent discontinuation	15 (11.6%)	13 (10.2%)	20 (15.6%)
AE leading to dose modification of study drug	14 (10.9%)	13 (10.2%)	21 (16.4%)
AE leading to interruption of study drug	14 (10.9%)	12 (9.4%)	21 (16.4%)
AE leading to dose reduction of study drug	0 (0.0%)	1 (0.8%)	0 (0.0%)
Any TEAE	113 (87.6%)	113 (88.3%)	116 (90.6%)
Severe	58 (45.0%)	41 (32.0%)	39 (30.5%)
Moderate	79 (61.2%)	67 (52.3%)	75 (58.6%)
Mild	98 (76.0%)	96 (75.0%)	100 (78.1%)
[Source: Reviewer's results. Abbreviations: N, number of subjects in treatment arm; n, Number of subjects with an event; CI, Confidence Interval; SAE, Serious Adverse Event]			

Deaths

All cause death was the primary endpoint. See analysis of deaths in the efficacy section 6.2.2. The most commonly reported on-treatment cause of death was Investigator-reported "disease under study" or CEC adjudicated "Pulmonary Arterial Hypertension." Although the noninferiority criteria was met, there was a numerical increase in the number of deaths (total and on-treatment) for the 5 mg group compared to 20 mg and 80 mg groups.

Table 17. Investigator-Reported Causes of Death

	Reason for Death[1]	Sildenafil 5 mg N = 129		Sildenafil 20 mg N = 128		Sildenafil 80 mg N = 128	
		n	%	N	%		%
Total Deaths	All Cause	34	26.4	25	19.5	19	14.8
On-treatment deaths[2]	Disease under study	16	12.4	7	5.5	11	8.6
	Other	9	7.0	6	4.7	4	3.1
	Unknown	0	0.0	1	0.8	1	0.8

Off-treatment deaths	Disease under study	4	3.1	8	6.3	2	1.6
	Other	10	7.8	6	4.7	1	0.8
	Unknown	0	0.0	1	0.8	1	0.8

[1] Investigator-reported cause of death. [2]On-treatment deaths are any deaths within 7 days of last dose.
[Source: Reviewer's results]

Table 18. Clinical Event Committee's Adjudicated Causes of Death

	Reason for Death[1]	Sildenafil 5 mg N = 129		Sildenafil 20 mg N = 128		Sildenafil 80 mg N = 128	
		n	%	N	%		%
On-treatment deaths[2]	Pulmonary Arterial Hypertension	11	8.5	5	3.9	7	5.5
	Cardiovascular	6	4.7	4	3.1	6	4.7
	Non-Cardiovascular	4	3.1	1	0.8	2	1.6
	Cause of Death Not Determined	1	0.8	3	2.3	0	0
Off-treatment deaths	Pulmonary Arterial Hypertension	7	5.4	6	4.7	1	0.8
	Cardiovascular	2	1.6	2	1.6	0	0
	Non-Cardiovascular	2	1.6	2	1.6	2	1.6
	Cause of Death Note Determined	1	0.8	2	1.6	1	0.8

[1]CEC-reported cause of death. [2]On-treatment deaths are any deaths within 7 days of last dose.
[Source: Reviewer's results]

Serious Adverse Events

Non-fatal SAEs that are study endpoints (i.e., hospitalization for worsening of PAH and clinical worsening) are shown in Table 8 (investigator-reported). Higher proportion of subjects in 5 mg TID group had adjudicated nonfatal clinical worsening events: 28% for 5 mg TID vs. 20% and 13% for 20 mg and 80 mg TID, respectively. A similar finding was observed for adjudicated clinical events (Applicant's Table 14.2.2.1.1.1).

A summary of all SAEs (> 5% subjects in at least 1 treatment group) grouped by either SMQs or FMQs is shown in Table 19. Higher proportion of subjects in 5 mg TID group had disease-specific SAEs such as Pulmonary Hypertension SMQ or Heart Failure FMQ/Cardiac Failure SMQ.

The proportion of subjects who discontinued from the study due to serious AEs was higher in the sildenafil 80 mg TID group (16% subjects) compared to the sildenafil 5 mg TID group (12% subjects) and the sildenafil 20 mg TID group (10% subjects). Treatment-related SAEs which led to permanent discontinuation were reported for 1 subject in the sildenafil 5 mg TID group (SAE

by preferred term: cardiac failure acute), 2 subjects in the sildenafil 20 mg TID group (SAE by preferred term: hypersensitivity vasculitis [2 events]), and 1 subject in the sildenafil 80 mg TID group (SAE by preferred term: blood loss anemia and condition aggravated).

Table 19. Serious SAEs by SMQ or FMQ in >5% Subjects in at least 1 Treatment Group

Treatment-Emergent SAEs[1]	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
	N=129	N=128	N=128
	n (%)	n (%)	n (%)
Standard MedDRA Query (Broad)[2]			
Pulmonary hypertension	29 (22.5%)	19 (14.8%)	14 (10.9%)
Cardiomyopathy	21 (16.3%)	14 (10.9%)	12 (9.4%)
Cardiac failure	23 (17.8%)	13 (10.2%)	11 (8.6%)
Drug reaction with eosinophilia and systemic symptoms syndrome	14 (10.9%)	9 (7.0%)	10 (7.8%)
Infective pneumonia	10 (7.8%)	9 (7.0%)	7 (5.5%)
Anaphylactic reaction	9 (7.0%)	8 (6.2%)	6 (4.7%)
Eosinophilic pneumonia	7 (5.4%)	10 (7.8%)	5 (3.9%)
Shock-associated circulatory or cardiac conditions (excl torsade de pointes)	9 (7.0%)	6 (4.7%)	6 (4.7%)
Acute central respiratory depression	8 (6.2%)	6 (4.7%)	6 (4.7%)
Opportunistic infections	7 (5.4%)	6 (4.7%)	3 (2.3%)
Hypersensitivity	7 (5.4%)	5 (3.9%)	2 (1.6%)
FDA Medical Query (Broad)[2]			
Heart Failure	27 (20.9%)	15 (11.7%)	13 (10.2%)
Myocardial Ischemia	7 (5.4%)	5 (3.9%)	1 (0.8%)
Bacterial Infection	16 (12.4%)	11 (8.6%)	11 (8.6%)
Pneumonia	10 (7.8%)	9 (7.0%)	7 (5.5%)
Viral Infection	13 (10.1%)	7 (5.5%)	6 (4.7%)

[1]Treatment-Emergent AEs defined as occurring within 7 days; [2]MedDRA v23.1 or FMQ Version v2 Abbreviations: N, number of subjects in treatment arm; n, Number of subjects with an event; CI, Confidence Interval; AE, Adverse Event. [Source: Reviewer's results]

Discontinuations Due to Adverse Effects

As shown in Table 16, the proportion of subjects who discontinued from the study due to TEAEs was higher in the sildenafil 80 mg TID group (16% subjects) compared to the sildenafil 5 mg TID group (12% subjects) and the sildenafil 20 mg TID group (10% subjects). The most commonly reported MedDRA 'system of organ class' (SOC) for discontinuation was Cardiac Disorders with overall 17 (4%) subjects, which included AEs of cardiac failure, cardio-respiratory arrest and cardiac arrest.

Safety Analyses by Dose Groups

A summary of the incidence of TEAEs occurring in ≥5% of subjects in either treatment group by PT is shown in Table 20. All treatment groups had similar number of subjects with TEAEs (Table 16). A higher risk for the treatment emergent event *headache* was associated with sildenafil 20 mg TID; the risk difference was 15 (95% CI: 4.1, 25.7) for the comparison of sildenafil 20 mg TID vs. sildenafil 5 mg TID. A higher risk was associated for the events *right ventricular failure*, *myalgia and PAH*; the risk differences were -8.5 (95% CI: -15.1, -3.2), 6.3 (95% CI: 0.39, 13.0) and -9.2 (95% CI: -18.0, -0.75), respectively, for the comparison of sildenafil 80 mg TID vs. sildenafil 5 mg TID. All other TEAEs had 95% CI that included zero for the risk difference, indicating similar risks across groups.

Table 20. Treatment Emergent AEs in **≥5%** of Subjects in at Least 1 Treatment Group by MedDRA Preferred Term

Preferred Term	Sildenafil 5 mg (N = 129)			Sildenafil 20 mg (N = 128)			Sildenafil 80 mg (N = 128)		
	Events	Number Subjects	(%)	Events	Number Subjects	(%)	Events	Number Subjects	(%)
Headache*	105	26	20.2	106	45	35.2	95	33	25.8
Diarrhoea	27	13	10.1	45	17	13.3	30	21	16.4
Oedema peripheral	18	14	10.9	25	17	13.3	9	8	6.3
Dizziness	17	12	9.3	22	16	12.5	30	18	14.1
Dyspnoea	21	15	11.6	36	16	12.5	22	14	10.9
Nasopharyngitis	44	19	14.7	34	16	12.5	40	19	14.8
Chest pain	9	7	5.4	32	15	11.7	73	14	10.9
Epistaxis	12	11	8.5	22	14	10.9	22	13	10.2
Pain in extremity	8	7	5.4	17	14	10.9	13	6	4.7
Pulmonary arterial hypertension**	38	24	18.6	24	14	10.9	15	12	9.4
Arthralgia	17	14	10.9	19	13	10.2	24	15	11.7
Bronchitis	17	12	9.3	13	13	10.2	11	11	8.6
Nausea	17	16	12.4	20	12	9.4	12	8	6.3
Back pain	20	16	12.4	25	11	8.6	23	14	10.9
Cough	24	14	10.9	14	11	8.6	25	12	9.4
Dyspepsia	9	6	4.7	12	10	7.8	24	10	7.8
Fatigue	19	11	8.5	17	10	7.8	18	9	7
Myalgia**	5	4	3.1	16	10	7.8	17	12	9.4
Vomiting	11	7	5.4	14	10	7.8	8	7	5.5
Influenza	8	6	4.7	13	9	7	16	11	8.6

Preferred Term	Sildenafil 5 mg (N = 129)			Sildenafil 20 mg (N = 128)			Sildenafil 80 mg (N = 128)		
	Events	Number Subjects	(%)	Events	Number Subjects	(%)	Events	Number Subjects	(%)
Pneumonia	15	11	8.5	9	9	7	9	8	6.3
Pyrexia	3	3	2.3	11	9	7	15	9	7
Upper respiratory tract infection	42	16	12.4	10	9	7	27	13	10.2
Cardiac failure	13	10	7.8	9	8	6.3	8	6	4.7
Abdominal pain upper	12	6	4.7	29	7	5.5	15	11	8.6
Asthenia	3	3	2.3	14	7	5.5	3	2	1.6
Hypokalaemia	12	10	7.8	9	6	4.7	7	5	3.9
Hypotension	11	9	7	6	6	4.7	15	7	5.5
Peripheral swelling	10	8	6.2	6	6	4.7	7	5	3.9
Right ventricular failure**	19	13	10.1	6	6	4.7	2	2	1.6
Respiratory tract infection viral	4	4	3.1	6	5	3.9	13	8	6.3
Nasal congestion	10	8	6.2	6	4	3.1	5	5	3.9
Respiratory tract infection	9	5	3.9	4	4	3.1	7	7	5.5
Anaemia	8	6	4.7	3	3	2.3	18	12	9.4
Sinusitis	7	3	2.3	6	3	2.3	17	10	7.8

[Source: Reviewer's results. Cross reference: Applicant's Table 28 in CSR*]*
Abbreviations: PT, preferred term MedDRA 23.1; * denotes higher risk detected with 20 mg TID; ** denotes higher risk detected with 5 mg TID

The majority of TEAEs were of mild or moderate intensity (Table 16). Severe TEAEs in ≥2% subjects are shown in Table 21. The 5 mg TID treatment group had more disease-related events of severe PAH, right heart failure and sudden death. The 80 mg TID group had more severe diarrhea events.

Table 21. Severe Treatment Emergent AEs in **≥2%** of Subjects in at Least 1 Treatment Group by MedDRA Preferred Term

Preferred Term	*Sildenafil 5 mg (N = 129)*			*Sildenafil 20 mg (N = 128)*			*Sildenafil 80 mg (N = 128)*		
	Events	*Number Subjects*	*(%)*	*Events*	*Number Subjects*	*(%)*	*Events*	*Number Subjects*	*(%)*
Total Severe TEAEs	*171*	*58*	*45.0*	*107*	*41*	*32.0*	*65*	*39*	*30.5*
Pulmonary arterial hypertension	10	10	7.8	10	7	5.5	3	3	2.3
Right ventricular failure	9	8	6.2	3	3	2.3	2	2	1.6
Pneumonia	6	5	3.9	3	3	2.3	1	1	0.8
Cardiac failure	4	4	3.1	6	5	3.9	2	2	1.6
Cardiac failure congestive	8	3	2.3	6	3	2.3	2	2	1.6
Dyspnoea	4	3	2.3	3	2	1.6	1	1	0.8
Sudden death	3	3	2.3	0	0	0	0	0	0
Pulmonary hypertension	2	2	1.6	4	4	3.1	2	2	1.6
Cardiac arrest	1	1	0.8	3	3	2.3	0	0	0
Hypoxia	1	1	0.8	5	3	2.3	0	0	0
Diarrhoea	1	1	0.8	0	0	0	4	4	3.1
Back pain	0	0	0	3	3	2.3	0	0	0
Nausea	0	0	0	4	3	2.3	1	1	0.8

[Reviewer's results. Cross reference: Applicant's Table 29 in CSR*]* Abbreviations: PT, preferred term MedDRA 23.1

8.2.2 Deaths and Serious Adverse Events in STARTS-2

Extent of Exposure

Total patient-year (p-y) exposure to sildenafil was 269 p-y, 371 p-y and 475 p-y for the low, medium and high dose groups, respectively.

Investigators were allowed to increase the sildenafil dose (up-titration) after Week 52, if the investigator believed the subject would benefit from a higher dose level. In the low dose group,

28/55 (51%) subject had doses increased and in the medium dose group, 12/74 (16%) subjects had doses increased.

Deaths

There were no deaths in the 16-week study (STARTS-1), but in the long-term extension study, STARTS-2, there was 42 deaths (Table 22, Figure 8). Of these 42 deaths, 28 were on treatment (within 7 days of the last dose) which included 3 in the low dose, 8 in the medium dose and 17 in the high dose. The time course for the on-treatment deaths do not suggest a dose-related increase until after one year of sildenafil treatment (Figure 10). Off-treatment deaths occurred between 9 days to 1202 days (median: 217 days) from the last sildenafil dose.

Table 22. Deaths by Sildenafil Dose Group (STARTS-2, Final)

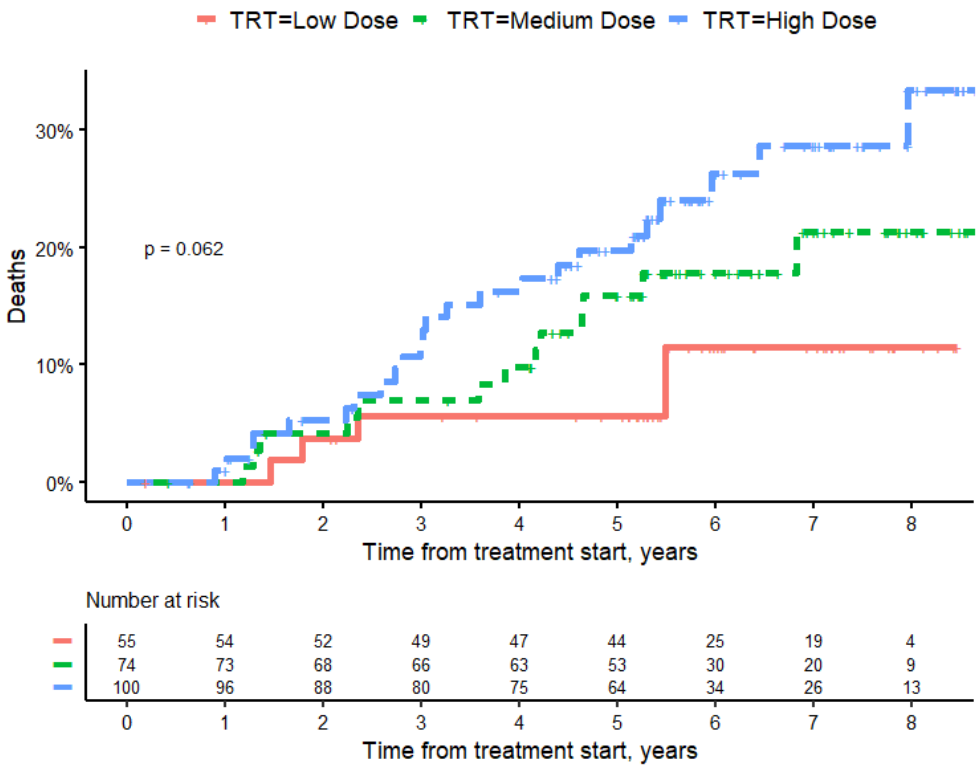
Dose		Deaths	Dose		Death	Overall Deaths (%)	Annualized Event Rate
Starts-1	Starts-2		Starts-1	Starts-2			
Low	Low	5/42	Placebo	Low	0/13	5/55 (9)	1.6% (0.2–3.0)
Medium	Medium	12/55	Placebo	Medium	1/19	13/74 (18)	3.2% (1.4–4.9)
High	High	19/77	Placebo	High	5/23	24/100 (24)	4.6% (2.8–6.4)
			Placebo	Not randomized	0/5	0/5	0

Reviewer's analysis. Source: adtte, Program R

Event rate = number of deaths/patient-year follow-up

Listing of all deaths is presented in Appendix 13.3.

Figure 8. Kaplan Meier Plot for All-Causality Deaths (STARTS-2, Final)

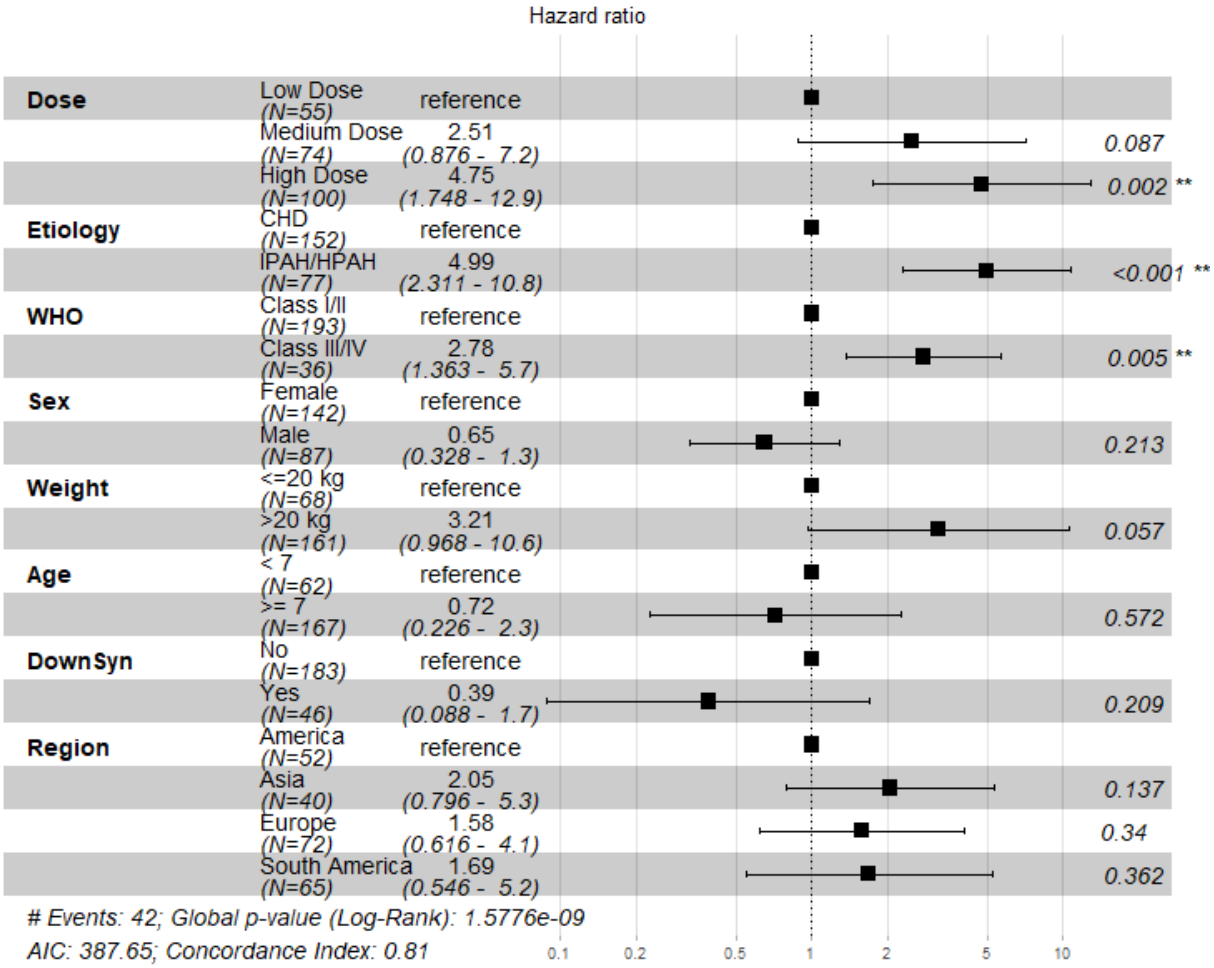


[Reviewer's analysis. Source: adtte, adident, Program: R. Note: Treatment start includes the 16-week delay in receipt of sildenafil for subjects randomized to placebo in STARTS-1.]

The pediatric population who died was largely comprised of an idiopathic PAH population with WHO functional class III/IV (Figure 9). This population is similar to the adult PAH population for which performance benefit has been demonstrated in SUPER trial[14] and reflected in the USPI.

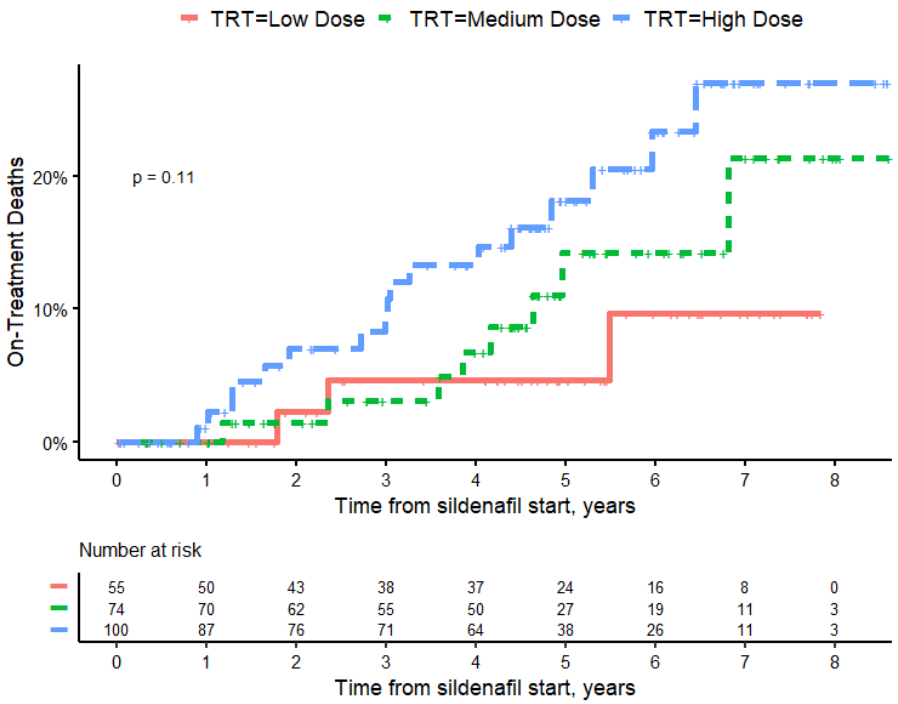
[14] Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension [published correction appears in N Engl J Med. 2006 Jun 1;354(22):2400-1]. N Engl J Med. 2005;353(20):2148-2157. doi:10.1056/NEJMoa050010

Figure 9. Subgroup Analysis For All-Cause Deaths by Baseline Characteristics (STARTS-2, Final)



[Reviewer's analysis. Source: adtte, adident Program: R. Abbreviations: WHO, WHO functional class, DOWNSYND, Down syndrome]

Figure 10. Kaplan-Meier Plot for On-Treatment Deaths (STARTS-2, Final)



[Reviewer's analysis. Source: adtte, adident, Program: R. In this plot, the censor time is the days on sildenafil treatment +7 days and the start of sildenafil treatment accounts for the 16-week delay in receipt of sildenafil for subjects randomized to placebo in STARTS-1.]

The Kaplan-Meier plot above does not indicate the actual dose the subject was taking at the time of death. After 52 weeks from the start of STARTS-1, the Investigator could increase the sildenafil dose due to loss of efficacy or a worsening of disease. Dose increases due to body weight were not considered up-titrations. Table 23 shows deaths by final dose while on study or at time of death. Although the high-dose sildenafil was associated with an increased risk of mortality when final dose was assessed, it is confounded by the ability for the Investigator to up-titrate for lack of efficacy/disease worsening. Furthermore, despite the increase in up-titrations in the low dose group, the deaths in this group remained low.

Table 23. Deaths by Actual Dose Group (STARTS-2, Final)

	Low Dose (N=55)	Medium Dose (N=74)	High Dose (N=100)
Total deaths	5 (9%)	13 (18%)	24 (24%)
Final dose Off-treatment	2/17 (8%)	5/24 (17%)	7/29 (24%)

	Low Dose (N=55)	Medium Dose (N=74)	High Dose (N=100)
Low	0/15 (0)	0/0 (0)	0/0 (0)
Medium	2/18 (11%)	5/41 (12%)	0/3 (0)
High	1/5 (20%)	3/9 (33%)	17/68 (25%)

[Source: Applicant's Table 14.4.2.5.4]

While increased mortality was observed in higher sildenafil doses compared with low dose, no apparent safety signal leading to death was noted. The causes of death did not indicate a specific drug-related cause and were consistent with progression of PAH disease and heart failure (see Appendix 13.3). The majority of deaths (76%) were associated with IPAH etiology, whereas only 33% of the overall study population were classified with this etiology. Subjects who died had more severe disease at baseline — subjects were classified as WHO functional class III or IV, had greater than the median baseline value of PVRI (15 Wood units/m2) and mPAP (62 mmHg), and had lower than the median baseline value of cardiac index (62 L/min/m2). However, adjusting for these baseline covariates in Cox proportional hazard model did not fully account for the increased mortality observed with high dose sildenafil.[15]

Serious Adverse Events

Higher percentage of subjects in the medium and high doses experienced on-treatment SAEs, fatal SAEs and SAEs which led to treatment discontinuation (Table 24).

Table 24. Summary of On-Treatment Fatal and Nonfatal Serous Adverse Events (Starts-2, Final)

	Low Dose (N=55)		Medium Dose (N=74)		High Dose (N=100)	
	n	%	n	%	n	%
Subjects with at least 1 SAE	14	25.5	37	50.0	48	48.0
Subjects with Fatal SAE	3	5.5	9	12.2	17	17.0
SAEs leading to discontinuation	1	1.8	7	9.5	8	8.0
Annualized Rate of SAE	6.2		10		10.1	

[15] Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014;129(19):1914-1923. doi:10.1161/CIRCULATIONAHA.113.005698

[Reviewer's results Shown as SAEs on treatment + 7 days. Cross-reference: Applicant's Table 30]

As shown in Table 25, the major imbalance in non-fatal SAEs between dose groups is infections, such as pneumonia and upper respiratory tract infections. Three subjects with infections discontinued the study (1 subject in each dose group). These infection SAEs were not considered related to sildenafil treatment.

> *Reviewer's comment: Patients with PAH are susceptible to upper respiratory tract infections and pneumonia; however, there is no clear explanation for the imbalance in these infections in the medium and high dose groups. Three subjects reported fatal infections: pneumonia (ID (b) (6) 80 mg TID), peritonitis (ID (b) (6) 20 mg TID) and urinary tract infection (ID (b) (6), 20 mg TID).*

Treatment-related, non-fatal SAEs occurred in 6 subjects: enterocolitis (ID (b) (6)) in the low dose; convulsion (ID (b) (6)) in the medium dose; and hypersensitivity and stridor (ID (b) (6)), hypoxia and neurosensory deafness (ID (b) (6)); ventricular arrhythmia (ID (b) (6)) in the high dose.

Table 25. Treatment-Emergent Serious Adverse Events in at Least 2 Subjects (Starts-2, Final)

MedDRA Higher Level Group Term	Sildenafil Low Dose (N=55)		Sildenafil Medium Dose (N=74		Sildenafil High Dose (N=100)	
Preferred Term	n	%	n	%	n	%
Infections - pathogen unspecified	*3*	*5.5*	*15*	*19.5*	*21*	*21*
Pneumonia	1	1.8	7	9.1	8	8.0
Upper respiratory tract infection	0	0	1	1.3	6	6.0
Gastroenteritis	0	0	3	3.9	3	3.0
Bronchitis	1	1.8	1	1.3	3	3.0
Bronchopneumonia	1	1.8	1	1.3	3	3.0
Urinary tract infection	0	0	0	0	2	2.0
Heart failures	*3*	*5.5*	*4*	*5.2*	*6*	*6.0*
Cardiac failure	1	1.8	2	2.6	4	4.0
Right ventricular failure	2	3.6	2	2.6	1	1.0
Cardiac failure congestive	1	1.8	0	0	1	1.0
Pulmonary vascular disorders	*2*	*3.6*	*3*	*3.9*	*7*	*7.0*
Pulmonary hypertension	1	1.8	3	3.9	5	5.0
Pulmonary arterial hypertension	0	0	0	0	3	3 0

MedDRA Higher Level Group Term	Sildenafil Low Dose (N=55)		Sildenafil Medium Dose (N=74		Sildenafil High Dose (N=100)	
Preferred Term	n	%	n	%	n	%
Neurological disorders NEC	*3*	*5.5*	*2*	*2.6*	*2*	*2.0*
Syncope	2	3.6	2	2.6	1	1.0
Respiratory disorders NEC	*1*	*1.8*	*2*	*2.6*	*4*	*4.0*
Haemoptysis	0	0	2	2.6	0	0
Hypoxia	0	0	0	0	2	2.0
Viral infectious disorders	*0*	*0*	*3*	*3.9*	*3*	*3.0*
Gastroenteritis viral	0	0	1	1.3	2	2.0
Bacterial infectious disorders	*1*	*1.8*	*1*	*1.3*	*2*	*2.0*
Bone and joint injuries	*1*	*1.8*	*3*	*3.9*	*0*	*0*
Cardiac arrhythmias	*1*	*1.8*	*1*	*1.3*	*2*	*2.0*
Dental and gingival conditions	*0*	*0*	*1*	*1.3*	*3*	*3.0*
General system disorders NEC	*3*	*5.5*	*0*	*0*	*1*	*1.0*
Chest pain	2	3.6	0	0	1	1.0
Body temperature conditions	*0*	*0*	*0*	*0*	*3*	*3.0*
Pyrexia	0	0	0	0	2	2.0
Exposures, chemical injuries and poisoning	*1*	*1.8*	*2*	*2.6*	*0*	*0*
Upper respiratory tract disorders (excl infections)	*0*	*0*	*1*	*1.3*	*2*	*2.0*
Cardiac and vascular investigations (excl enzyme tests)	*0*	*0*	*2*	*2.6*	*0*	*0*
Gastrointestinal motility and defaecation conditions	*0*	*0*	*2*	*2.6*	*0*	*0*
Diarrhoea	0	0	2	2.6	0	0

[Source: Reviewer's results. Shown as SAEs on treatment + 7 days. Coded using MedDRA v15.1]

Fourteen subjects experienced SAE that led to permanent discontinuation from study treatment. These discontinuations were mainly considered to be related to the disease under study. AEs that were considered to be related to study drug included episodes of convulsion, stridor, neurosensory deafness, and hypoxia.

Reviewer's comment: The Applicant reports 12 subject experienced SAE that led to permanent discontinuation from study treatment.

Table 26. Serious Adverse Events Leading to Discontinuation (Starts-2, Final)

Preferred Term	Sildenafil Low Dose (N=55)		Sildenafil Medium Dose (N=74		Sildenafil High Dose (N=100)	
	n	%	n	%	n	%
All discontinuations due to SAEs	*1*	*1.8*	*6*	*8.1*	*7*	*7.0*
Cardiac failure	1	1.8	0	0	2	2.0
Gingivitis	1	1.8	0	0	0	0
Pneumonia	0	0	1	1.3	0	0
Upper respiratory tract infection	0	0	0	0	1	1.0
Cough	0	0	0	0	1	1.0
Dyspnoea exertional	0	0	0	0	1	1.0
Haemoptysis	0	0	1	1.3	0	0
Hypoxia*	0	0	0	0	1	1
Foetal exposure during pregnancy	0	0	1	1.3	0	0
Toxicity to various agents	0	0	1	1.3	0	0
Hypersensitivity	0	0	0	0	1	1
Skull fracture	0	0	1	1.3	0	0
Cardiac operation	0	0	1	1.3	0	0
Deafness neurosensory*	0	0	0	0	1	1
Contusion	0	0	1	1.3	0	0
Subdural haematoma	0	0	1	1.3	0	0
Syncope	0	0	1	1.3	0	0
Pulmonary hypertension	0	0	0	0	1	1
Convulsion*	0	0	1	1.3	0	0
Stridor*	0	0	0	0	1	1

[Source: Reviewer's results. Shown as SAEs on treatment + 7 days. Coded using MedDRA v15.1. *Considered treatment-related SAEs.

8.2.3 Safety in the Postmarket Setting

Safety Database

Sildenafil was approved for the treatment of PAH in pediatric subjects, aged 1-17 years, in Europe (2011), Japan (2017) and Indonesia (2019). It is marketed as tablets (20 mg) and powder for oral suspension (POS; 10 mg/ml) at recommended doses of:

- Subjects weighing ≤ 20 kg, 10 mg (1 mL of oral suspension) TID;
- Subjects weighing > 20 kg, 20 mg (20 mg tablet or 2 mL of oral suspension) TID.

Applicant's cumulative safety database contains cases of adverse events reported spontaneously to the Applicant, cases reported by the health authorities, cases published in the medical literature, cases from Applicant's marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality.

Safety Concerns Identified Through Postmarket Experience

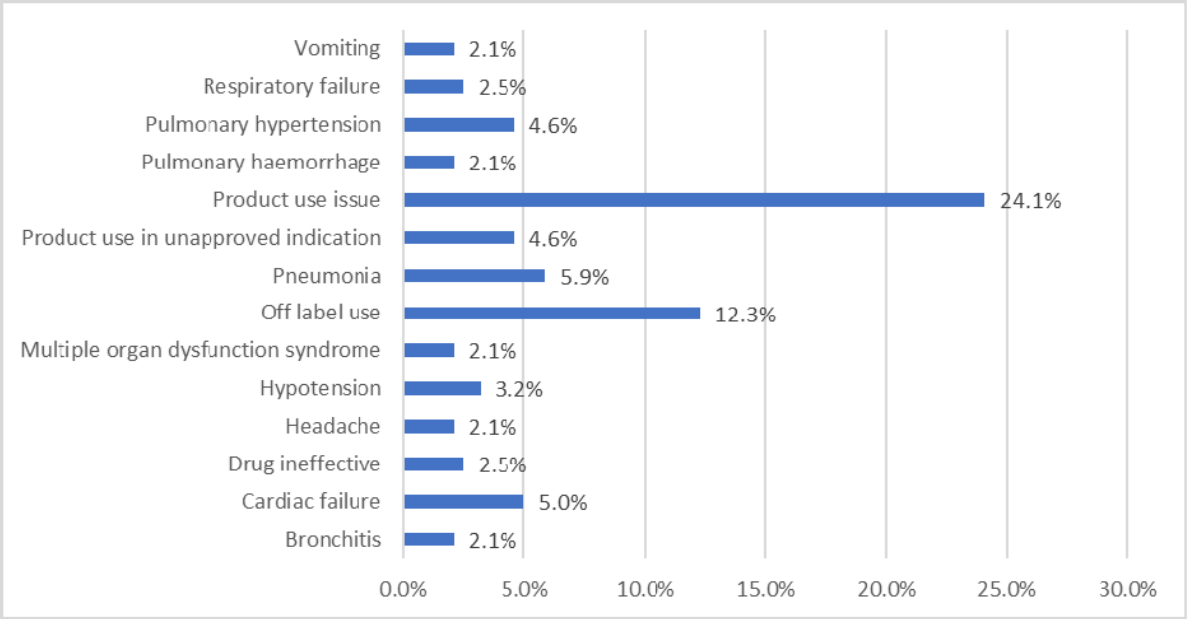
There was a total of 439 cases (including 799 events) reported for sildenafil use in pediatric subjects, 1–17 years, for the treatment of PAH through 30 November 2021.

- 278 cases considered serious in nature
- 95 cases resulted in a fatal outcome
- 105 cases recovered
- 50 cases were recovering at the time of the report
- 28 cases the outcome was not recovered

The countries that reported the most events (>20 cases) were Japan (208), US (48), Germany (29) and China (23). Sources of reports included clinical study (213), spontaneous (179), literature reports (40) and other solicited reports (7).

Figure 11 shows the MedDRA Preferred Terms reported in ≥2% of cases (serious and non-serious). No new safety information has been identified from these cases.

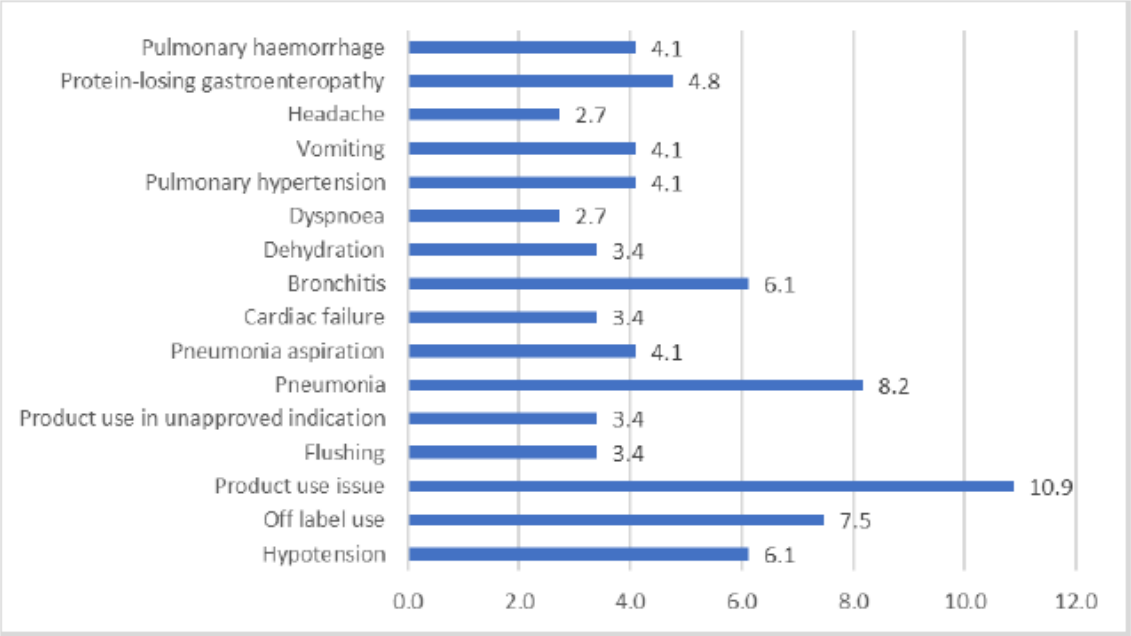
Figure 11. Adverse Events in Postmarket Database **(≥2%** cases)



[Source: Applicant's Figure 1 in Cumulative Safety Report for Revatio Use in Paediatric Subjects for Pulmonary Arterial Hypertension]

There were 147 cases reporting serious adverse events other than death during postmarketing, involving 73 females and 68 males, where gender was reported, with ages ranging from 1 day to 17 years. Figure 12 shows the most commonly reported serious adverse events reported (2% of cases). No new safety information has been identified from these cases.

Figure 12. Serious Adverse Events in Postmarket Database **(≥2%** cases)



[Source: Applicant's Figure 2 in Cumulative Safety Report for Revatio Use in Paediatric Subjects for Pulmonary Arterial Hypertension]

> *Reviewer's comment: Considering the underlying disease of the subject population, these are not unexpected serious adverse events. Known adverse events with sildenafil include hypotension, vision and hearing loss, epistaxis, headache, dyspepsia and flushing.*

Postmarketing Study A1481263

A1481263 is a non-interventional study in Japan conducted as a regulatory post marketing commitment plan.[16] This was conducted as a surveillance study with the objectives to collect information about: (1) adverse drug reactions not expected based on the local product document (unknown adverse drug reaction), (2) the incidence of adverse drug reactions in this surveillance and (3) factors considered to affect the safety and/or efficacy of this drug. The study included subjects for whom an investigator prescribed sildenafil for PAH, irrespective of age, and were followed for a period of 3 years following first administration.

[16] https://clinicaltrials.gov/ct2/show/study/NCT00666198

A total of 3304 subjects were included in this study, of which 1050 were in subjects <15 years of age. There were 71 cases with fatal outcomes. Age ranged from 1 day to 17 years and included 40 males and 37 females. Subjects had significant medical histories: cardiovascular disorders, cholestasis, bronchopulmonary dysplasia, PAH, atrial septal defect, patent ductus arteriosus. Sixty-nine (69) of the subjects had multiple concomitant medications including (but not limited to) aspirin, bosentan, furosemide, dopamine, epoprostenol, enalapril, alprostadil. For the majority of cases (68/71), the events leading to a fatal outcome were related to the progression of underlying disease and/or developments of infections and were considered unrelated to sildenafil by the Investigator. For 3 cases, the Investigator considered that the events preceding to or potentially contributing to the fatal outcome were at least possibly related to sildenafil. These cases included 1) hypotension which is a known adverse reaction but the cause of death was cardiac failure and associated with underlying disease APAH; 2) hypotension but the cause of death was pneumonia; and 3) hypoxia but cause of death was Disseminated Intravascular Coagulation and multiple organ failure.

Reviewer's comment: The results of this study have not been published.

8.3 Discussion of Safety Issues

8.3.1 Safety in the Pediatric PAH Population

While increased mortality in pediatrics was observed in higher sildenafil doses compared with low dose, no apparent safety signal leading to death was noted. The causes of death did not indicate a specific drug-related cause and were consistent with progression of PAH disease and heart failure. There was also no pattern in the adverse events or discontinuations that suggests a drug-related cause to the mortality events.

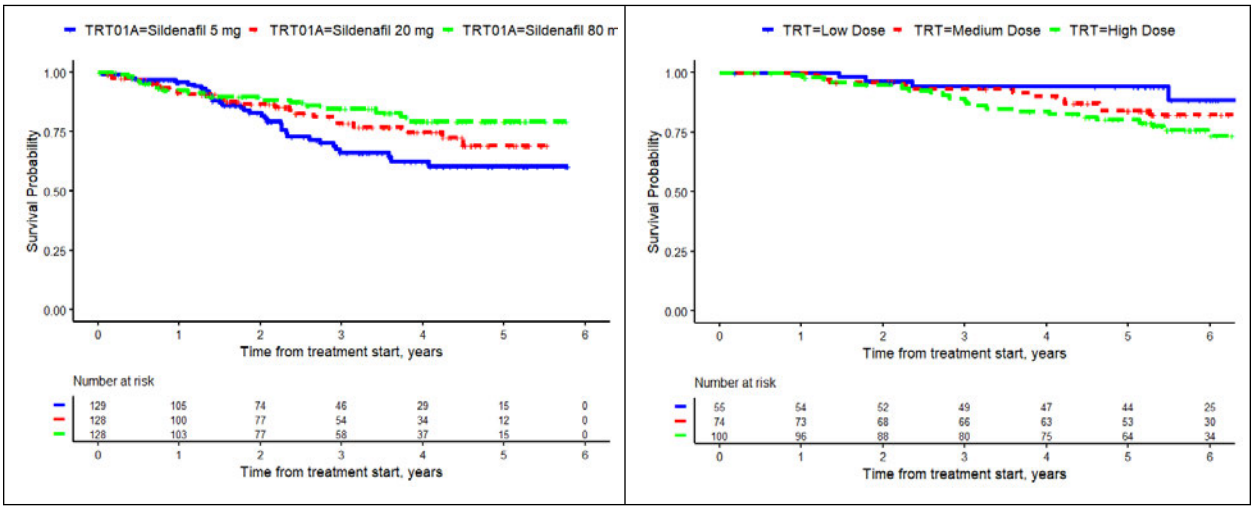
Post-marketing safety data have not revealed any new safety findings in pediatrics. Safety database is based on clinical experience of sildenafil at low doses (10 mg TID ≤20 kg; 20 mg TID > 20 kg) which was approved for the treatment of PAH in pediatric subjects in Europe (2011), Japan (2017) and Indonesia (2019). Furthermore, there is no corroborating safety signal for death in over 10 years clinical experience with off-label use of sildenafil in the pediatric population. In the US, sildenafil is extensively used off-label in pediatrics. Clinical practice guidelines from American Heart Association and American Thoracic Society recommends the use of sildenafil in the treatment of pediatrics with PAH despite the dose-response increase in deaths in STARTS-2 and in the product labeling.[17]

[17] Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99. 10.1161/CIR.0000000000000329

Controlled long-term survival benefit in the adult population with PAH was demonstrated in A1481324. The observed 5-year survival rates for the adult PAH were 60%, 69% and 79% for the 5 mg, 20 mg and 80 mg TID doses in the overall population. Survival benefit in the 80 mg TID dose was shown for the treatment naïve and IPAH subgroups.

The survival rates for all doses in the pediatric population in STARTS-2 were no worse than the survival rates in the overall adult populations in A1481324 (Figure 13). The 5-year survival rates in pediatrics ranged between 79% to 94% across the high to low dose groups. The pediatric subjects who died were largely comprised of IPAH etiology which is the same etiology for which survival benefit was demonstrated in A1481324. Furthermore, the pediatric subjects who died had more severe disease at baseline as classified as WHO function class III-IV. The adult PAH population comprised primarily of subjects classified as WHO function class III-IV (59%).

Figure 13. Kaplan-Meier Plot of Survival by Treatment Group for Overall Adult Population (left plot) and Pediatric Population (right plot)



[Source: Reviewer's results]

Persistence of benefit in the adult population with PAH was also shown in A1481324. As discussed above, the 20 mg and 80 mg TID doses showed delay in clinical worsening compared to the 5 mg dose. Prior to A1481324, clinical benefit of sildenafil monotherapy in adults was limited to 16-week increase in exercise capacity. Furthermore, A1481324 showed persistence in exercise capacity at 6- and 12-months (Table 10).

Overall, there is uncertainty about the dose-response in deaths in STARTS-2, and the increase in deaths in the high dose group cannot be explained. A1481324 provides data which show 1) controlled long-term survival benefit and 2) persistence of clinical benefit in a highly related adult PAH population.

8.3.2 Safety of the 5 mg TID Dose in Adults with PAH

Subjects in the sildenafil 5 mg TID group had a shorter extent of exposure, with a median duration of 645 dosing days compared to 741 dosing days with sildenafil 20 mg TID group and 910 dosing days with sildenafil 80 mg TID group. The sildenafil 5 mg TID group showed a higher observed number of deaths, SAEs and severe AEs.

- The number of deaths was higher in the sildenafil 5 mg TID group (26% subjects) compared to the sildenafil 20 mg TID group (20% subjects) and the sildenafil 80 mg TID group (15% subjects). The most commonly reported cause of death was disease under study.
- The incidence of SAEs was highest in the sildenafil 5 mg TID group (51% subjects) compared to the sildenafil 20 mg TID group (38% subjects) and the sildenafil 80 mg TID group (40% subjects).
- The incidence of severe TEAEs was highest in the sildenafil 5 mg TID group (46% subjects) compared to the sildenafil 20 mg TID group (32% subjects) and the sildenafil 80 mg TID group (31% subjects).

9 Advisory Committee Meeting and Other External Consultations

The review team planned to discuss this application with the AC. Specifically, the team was seeking input on whether the favorable mortality results for the 20 mg and 80 mg TID dosing regimens in A1481324 in adult subjects with PAH mitigates the safety concern for dose-response increase in deaths in the pediatric PAH population in STARTS-2. However, the AC meeting was cancelled by DCN because clinical experts who treat pediatric PAH subjects were not available.

10 Labeling Recommendations

Suggestions for labeling were included directly in the draft label.

11 Risk Evaluation and Mitigation Strategies (REMS)

There is no REMS needed for sildenafil use in adults or children. Sildenafil's risks can be adequately managed in the postmarket setting through product labeling alone and that additional requirements are not necessary to maintain a favorable benefit-risk balance.

12 Postmarketing Requirements and Commitments

The clinical and statistical teams are not recommending any post-marketing studies.

13 Appendices

13.1 References

Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society [published correction appears in Circulation. 2016 Jan 26;133(4):e368]. Circulation. 2015;132(21):2037-2099. doi:10.1161/CIR.0000000000000329

Al-Naamani N, Paulus JK, Roberts KE, et al. Racial and ethnic differences in pulmonary arterial hypertension. Pulm Circ. 2017;7(4):793-796. doi:10.1177/2045893217732213

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Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation. 2014;129(19):1914-1923. doi:10.1161/CIRCULATIONAHA.113.005698

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FDA Statement: https://www.acc.org/latest-in-cardiology/articles/2014/04/14/11/18/fda-issues-clarification-on-sildenafil-use-in-children-with-pah

13.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): A Multinational, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults With Pulmonary Arterial Hypertension (PAH), A1481324

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 112		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3 Listing of Deaths in STARTS-2

Table 35: Listing of All Deaths by A1481131/A1481156 Treatment Sequence

Subject Number	Country	Gender + Age at Death (years)	Funct Class Rand[a]	Random Dose (A1481156)	Wt. (kg) Rand	Last Dose	Wt. (kg) Last	Days on Last Dose	Study Day of Last Dose	Study Day of Death	Years in A1481131 And A1481156	Difference in Days between Last Dose and Death	Cause of Death	Disease
LOW/LOW DOSE														
(b) (6)	Poland	F/17	III	10	37	40	49	377	2001	2002	5.5	1	Cardiac arrest/ Severe Pulmonary Hypertension	Primary PAH
	India	F/13	III	10	32	10	30	127	128	534	1.5	406	Reported death/No further information available	Secondary PAH/ Surgery
	India	M/11	III	10	21	40	23	30	651	651	1.8	0	Cardiac failure	Primary PAH
	Poland	F/17	III	10	62	40	52	524	1976	2004	5.5	28	Pulmonary hemorrhage	Primary PAH
	Hungary	M/18	I	10	58	40	53	413	861	861	2.4	0	Cardiac failure/Respiratory failure	Secondary PAH/ Surgery
MED/MED DOSE														
(b) (6)	India	F/6	II	10	15	10	17	363	363	492	1.3	129	Reported death/No other information available	Primary PAH
	Poland	M/13	III	20	43	40	50	311	429	430	1.2	1	Pulmonary hemorrhage	Primary PAH
	India	F/14	III	20	23	40	39	60	1692	1693	4.6	1	Cardiogenic shock	Primary PAH
	India	M/18	II	20	32	20	38	852	860	861	2.4	1	Sudden death/ Pulmonary Hypertension	Primary PAH
	Russian Federation	F/20	II	20	32	20	46	410	2488	2489	6.5	1	Duodenal ulcer perforation/ Peritonitis	Primary PAH

Subject Number	Country	Gender + Age at Death (years)	Funct Class Rand[a]	Random Dose (A1481156)	Wt. (kg) Rand	Last Dose	Wt. (kg) Last	Days on Last Dose	Study Day of Last Dose	Study Day of Death	Years in A1481131 And A1481156	Difference in Days between Last Dose and Death	Cause of Death	Disease
(b) (6)	India	F/18	III	20	42	40	31	286	1308	1308	3.6	0	Worsening Pulmonary Hypertension	Primary PAH
	Colombia	M/20	III	20	34	20	47	28	1626	1697	4.6	71	Cardiogenic shock//Worsening PAH	Primary PAH
	Guatemala	F/12	II	20	24	20	35	59	1521	1521	4.2	0	Sudden death/Worsening PAH	Primary PAH
	Brazil	M/15	IV	20	39	20	40	443	462	471	1.3	9	Cardiac failure	Primary PAH
	United States	F/13	I	40	60	40	59	523	531	820	2.2	289	Reported death/ Worsening PAH	Primary PAH
	Mexico	F/19	I	40	45	40	47	1212	1407	1407	3.9	0	Sudden death/ Pulmonary Artery Hypertension	Secondary PAH/ Surgery
	Poland	M/20	II	40	106	40	87	1246	1253	1540	4.2	287	Lung Transplant rejection/Renal failure	Primary PAH
HIGH/HIGH DOSE														
(b) (6)	Malaysia	F/7	II	20	16	20	17	317	324	324	0.9	0	Progression PAH/Respiratory arrest	Secondary PAH/ Congenital
	India	F/7	II	20	16	40	20	308	1100	1101	3.0	1	Sudden cardiac death	Primary PAH
	India	F/8	II	20	14	20	13	275	287	1027	2.8	740	Reported death/No further data	Primary PAH
	Mexico	F/9	II	20	16	20	14	1105	1112	1112	3.0	0	Cardiac arrest/ Cardiogenic shock	Primary PAH

Subject Number	Country	Gender + Age at Death (years)	Funct Class Rand[a]	Random Dose (A1481156)	Wt. (kg) Rand	Last Dose	Wt. (kg) Last	Days on Last Dose	Study Day of Last Dose	Study Day of Death	Years in A1481131 And A1481156	Difference in Days between Last Dose and Death	Cause of Death	Disease
(b) (6)	Colombia	F/3	II	20	9	20	11	361	369	370	1.0	1	Worsening Pulmonary Hypertension	Primary PAH
	India	M/19	II	40	35	40	37	765	781	1983	5.4	1202	Reported death/No further data	Primary PAH
	India	F/12	III	40	27	40	31	463	470	471	1.3	1	Cardiac failure	Primary PAH
	Russian Federation	F/14	III	40	27	40	34	597	603	604	1.7	1	Ventricular fibrillation	Secondary PAH/ Surgery
	Poland	F/16	II	40	41	80	46	641	1254	1314	3.6	60	Reported death/ PAH	Primary PAH
	Poland	M/16	III	40	36	80	54	660	1191	1191	3.3	0	Worsening Pulmonary Artery Hypertension	Primary PAH
	Mexico	F/15	II	40	26	40	43	9	1602	1602	4.4	0	Cardiogenic shock/ Pneumonia	Primary PAH
	Colombia	F/16	II	40	28	40	37	987	994	995	2.7	1	Reported death/ Cardiac failure	Secondary PAH/ Congenital
	Russian Federation	F/11	II	40	23	80	49	400	2351	2351	6.4	0	Cardiac arrest/ Worsening PAH	Primary PAH
	Hungary	M/11	I	40	21	80	45	48	2178	2178	6.0	0	Pneumonia	Primary PAH
	Mexico	F/9	II	40	26	40	22	786	794	941	2.6	147	Reported death/ Worsening Pulmonary Artery Hypertension	Primary PAH

Subject Number	Country	Gender + Age at Death (years)	Funct Class Rand[a]	Random Dose (A1481156)	Wt. (kg) Rand	Last Dose	Wt. (kg) Last	Days on Last Dose	Study Day of Last Dose	Study Day of Death	Years in A1481131 And A1481156	Difference in Days between Last Dose and Death	Cause of Death	Disease
(b) (6)	Hungary	F/16	I	40	44	80	57	1357	1469	1470	4.0	1	Pulmonary embolism	Secondary PAH/ Congenital
	Poland	M/14	III	40	29	40	35	460	467	469	1.3	2	Cardiac failure	Secondary PAH/ Congenital
	India	F/20	II	80	49	80	58	1925	1932	1933	5.3	1	Reported death/PAH	Primary PAH
	India	F/19	III	80	50	80	48	1086	1093	1093	3.0	0	Cardiac failure	Primary PAH
PLBO/MED DOSE														
(b) (6)	Mexico	F/13	II	20	22	40	26	1179	1921	1921	5.3	0	Cardiac failure/PAH	Primary PAH
PLBO/HIGH DOSE														
(b) (6)	Hungary	F/14	I	20	14	40	26	628	2167	2908	8.0	741	Reported death/No further data	Primary PAH
	United States	F/15	II	40	35	40	36	325	449	846	2.3	397	Reported Death/PAH/ No further information available	Secondary PAH/ Congenital
	Colombia	F/12	I	40	32	40	45	696	815	815	2.2	0	Respiratory arrest/Penicillin allergy	Primary PAH
	Russian Federation	M/14	III	40	25	80	46	250	1874	1874	5.1	0	Sudden death/ Suspected ventricular fibrillation	Primary PAH

Subject Number	Country	Gender + Age at Death (years)	Funct Class Rand[a]	Random Dose (A1481156)	Wt. (kg) Rand	Last Dose	Wt. (kg) Last	Days on Last Dose	Study Day of Last Dose	Study Day of Death	Years in A1481131 And A1481156	Difference in Days between Last Dose and Death	Cause of Death	Disease
(b) (6)	Colombia	M/19	II	80	58	20	68	144	1669	1683	4.6	14	Cardiac arrest/ Cardiac + Respiratory failure	Secondary PAH/ Surgery

[a] *WHO Functional Class at randomization for Study A1481131.*
Source: Table 14.3.2.1, Narratives for subjects who died and A1481131 CSR Erratum 2
Deaths that occurred within 7 days of last study treatment are considered on-treatment death, otherwise are off-treatment death.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE E GARNETT
01/31/2023 09:47:59 AM

STEVE G BAI
01/31/2023 09:51:45 AM

JIALU ZHANG
01/31/2023 10:00:20 AM

FORTUNATO F SENATORE
01/31/2023 10:31:29 AM

NORMAN L STOCKBRIDGE
01/31/2023 10:46:05 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021845Orig1s025

OTHER REVIEW(S)

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA:	021845/S-025
Drug:	Revatio (sildenafil citrate)
Class:	Phosphodiesterase-5 (PDE-5) inhibitor
Applicant:	Viatris Specialty LLC
Supplement description:	This efficacy supplement provides for changes to labeling to include a new indication based on the results of postmarketing requirement (PMR) study No. A1481324, titled "A Multinational, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with Pulmonary Arterial Hypertension (PAH)". Furthermore, the Applicant is seeking (b) (4)
Proposed New Indication:	(b) (4)
Approved Indication:	REVATIO is indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise.
Date of Submission:	March 31, 2022
FDA Received Date:	March 31, 2022
Approval date:	January 31, 2023
PDUFA date:	January 31, 2023

❖ REVIEW TEAM

Center for Drug Evaluation and Research

- ❖ Office of New Drugs
  - *Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiology and Nephrology (DCN)*
    - Norman Stockbridge, MD, PhD – Division Director
    - Mary Ross Southworth, PharmD – Deputy Director for Safety
    - Michael Monteleone, MS, RAC – Associate Director for Labeling
    - Fortunato Senatore, MD, PhD – Cross Discipline Team Leader
    - Christine Garnett, PharmD – Clinical Reviewer

- Office of Translational Sciences
  - *Office of Biostatistics, Division of Biometrics II*
    - Jialu Zhang, PhD (Team Leader)
    - Steven Bai, PhD (Reviewer)
  - *Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology*
    - Snehal Samant, PhD – Clinical Pharmacology Team Leader
    - Xiaomeng Xu, PhD – Clinical Pharmacology Reviewer
  - *Office of Clinical Pharmacology, Division of Pharmacometrics*
    - Liang Li, PhD – Pharmacometrics Team Leader
    - Jihye Ahn, PhD – Pharmacometrics Reviewer
- Office of Pharmaceutical Quality
  - *Office of Lifecycle Drug Products, Division of Post-Marketing Activities I*
    - Gurpreet Gill-Sangha, PhD – Branch Chief
    - Santhosh Kalpathy, PhD – CMC Reviewer
- Office of Regulatory Operations
  - *Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology*
    - Brian Cooney, MS, PSM – Regulatory Health Project Manager
    - Alexis Childers, RAC, CQIA – Chief, Project Management Staff (Acting)
- Office of Surveillance and Epidemiology
  - *Office of Medical Error Prevention and Risk Management, Division of Medical Error Prevention and Analysis II*
    - Hina Mehta, PharmD – Reviewer
  - *Office of Medical Error Prevention and Risk Management, Division of Risk Management*
    - Yasmeen Abou-Sayed, PharmD – Team Leader
    - Brian Caruth, PharmD, BCPS – Reviewer
  - *Office of Pharmacovigilance and Epidemiology, Division of Epidemiology 2*
    - Mingfeng Zhang, MD, PhD – Team Leader
    - Margie Goulding, PhD – Epidemiologist
  - *Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigilance I*
    - Daniel Woronow, MD – Team Leader
    - Courtney Suggs PharmD, MPH – Safety Evaluator
  - *Project Management Staff*
    - Darrell Lyons, RN, BSN – Senior Regulatory Health Project Manager (Team Leader)
    - Monique Killen, PharmD – Senior Regulatory Health Project Manager
- Office of Medical Policy
  - *Office of Prescription Drug Promotion*
    - Charuni Shah, PharmD – Regulatory Review Officer
  - *Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling Team*
    - LaShawn Griffiths, MSHS-PH, BSN, RN – Associate Director for Patient Labeling

- Sharon R. Mills, BSN, RN, CCRP – Reviewer (Acting Team Leader)
- Jessica Chung, PharmD, MS – Reviewer

- *Office of Medical Policy Initiatives, Division of Medical Policy Programs*
  - Brantley Dorch, PharmD – Senior Project Manager

❖ BACKGROUND

Revatio (sildenafil citrate), originally developed by Pfizer, Inc., (Pfizer) is an inhibitor of cyclic guanosine monophosphate (cGMP) phosphodiesterase type 5 (PDE-5). Sildenafil increases cGMP, which can lead to vasodilation of the pulmonary vascular bed and systemically.

Revatio was first approved as a tablet formulation for the treatment of pulmonary arterial hypertension (PAH) on June 3, 2005 (NDA 021845). The approval for Revatio was based on study No. A1481140, a 12-week multinational, multi-center, randomized, double-blind, double-dummy, placebo-controlled clinical trial designed to assess the efficacy and safety of 3 doses of oral sildenafil (20, 40, and 80 mg TID) for the treatment of PAH to improve exercise ability. Revatio was subsequently approved for the treatment of PAH to delay clinical worsening (NDA 021845/S-006) on May 7, 2009, and as a new injection formulation (NDA 022473) on November 18, 2009.

In December 2001, FDA issued a Pediatric Written Request for Pfizer to conduct a pediatric development program for sildenafil. In August 2003, Pfizer initiated their pediatric development program (IND 063175) which included a 16-week phase 3 study No. A1481131, entitled "A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension" (STARTS-1). Pfizer then conducted a randomized long-term extension study No. A1481156, entitled "A Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131" (STARTS-2). On July 28, 2011, sildenafil received orphan-drug designation for "the treatment of pediatric (defined as children less than 17 years of age) pulmonary arterial hypertension".

In response to the Written Request, NDA 203109 was submitted on November 30, 2011, providing for a new dosage form (powder for oral suspension) and contained data obtained from pediatric studies STARTS-1 and STARTS-2 to expand the current indication to include a new pediatric indication for the treatment of PAH. In addition, on November 30, 2011, Pfizer submitted a combined application, cross referencing NDA 203109 with sNDA 021845/S-008 (tablets) and sNDA 022473/S-003 (injection), to include the newly proposed pediatric indication for each application and to harmonize all three dosage forms under one label. During the review cycle, pediatric exclusivity was granted on February 9, 2012 (refer to Memo dated February 10, 2012). Upon review, FDA identified an observed dose-response increase in mortality of patients within the STARTS-2 study. On August 30, 2012, NDA 203109, sNDA 021845/S-008, and sNDA 022473/S-003 were approved to include the new dosage form (powder for oral suspension) within the harmonized label; although, the new pediatric indication was not approved. In addition, the following labeling changes were implemented:

- Addition of study design and results of STARTS-1 and STARTS-2 in section 8.4.
- Revision of Section 1 "Indications and Usage" to include that Revatio is indicated for the treatment of PAH in adults to improve exercise ability and delay clinical worsening, and that the established effectiveness was short-term (12 to 16 weeks).
- A new warning under section 5.1 "Mortality with Pediatric Use", which stated: "In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing Revatio dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of Revatio, particularly chronic use, is not recommended in children."

Based on the increase in mortality observed in STARTS-2, a postmarketing requirement (PMR) was issued under NDA 021845 on June 7, 2013 (PMR 2026-1) requiring Pfizer to conduct a clinical study to

assess a signal of increased mortality when taking a high dose of Revatio compared to those taking a lower dose. To meet the PMR requirement, under IND 064924, Pfizer initiated PMR study No. A1481324 (AFFILIATE), entitled "A Multinational, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with Pulmonary Arterial Hypertension (PAH)" on September 22, 2014 (First Subject First Visit). The primary efficacy endpoint was the time to death (overall survival), as the purpose was to rule out the doubling of mortality between the 5 mg and 80 mg TID dose groups. The study enrolled 381 (89%) of 429 patients planned. The Last Subject Last Visit in all participating countries occurred on February 26, 2021.

On June 7, 2021, the Division of Cardiology and Nephrology (DCN) held an informal teleconference with Pfizer to discuss results from study A1481324. During this meeting, FDA agreed with Pfizer's proposal to submit an efficacy supplement to NDA 021845 proposing a new indication for Revatio to treat pediatric patients (1 to 17 years of age) with PAH, (b) (4) (b) (4) based on the final results of study A1481324 showing fewer events of clinical worsening in the 80 mg cohort.

DCN held a pre-sNDA meeting with Pfizer to discuss the final structure, content, format, and data presentation of this proposed sNDA (IND 064924; minutes dated November 24, 2021). During this meeting, Pfizer requested further input (b) (4) This teleconference was originally scheduled for September 20, 2021; however, per Pfizer's request dated September 20, 2021, this meeting was postponed to November 4, 2021. During this meeting, FDA agreed to engage in further technical discussions with Pfizer's statistical team regarding concerns FDA raised about the statistical analysis of Study A1481324 (refer to Section 2.2 Additional Comments). A follow-up meeting (informal teleconference) was held between FDA and Pfizer on December 15, 2021 (refer to Advice Letter dated January 3, 2022).

On June 15, 2020, NDA 021845 was transferred from Pfizer Inc. to Upjohn US 1 LLC (a subsidiary of Pfizer Inc). On January 26, 2022, the corporate name/address for NDA 021845 was changed from Upjohn US 1 LLC to Viatris Specialty LLC (the Applicant). On March 31, 2022, the Applicant submitted NDA 021845/S-025 which provided for the following:

- A new pediatric indication, (b) (4) (b) (4)

To support this sNDA, the Applicant submitted data from PMR study No. A1481324, along with cross-referenced information from previously submitted clinical study reports (STARTS-1 and STARTS-2) under NDA 021845 (tablet), NDA 203109 (powder for oral suspension), and NDA 022473 (solution for injection). The application was filed on May 30, 2022. During the review, the review team determined that Study No. A1481324 (adult PAH subjects) demonstrated a treatment effect by reducing mortality for the 20 mg and 80 mg doses compared to the 5 mg dose. The basis of substantial evidence of efficacy rests with the STARTS-1 trial and extrapolatory data from study No. A1481324 in adults via bridging strategy of pulmonary vascular resistance index (PVRI) to the pediatric population.

FDA's revisions to labeling [Package Insert (PI), Patient Package Insert (PPI), and Instructions for Use (IFU)] were sent to the Applicant on January 6, 2023. Two labeling meetings (teleconference) occurred between FDA and the Applicant on January 18 and 27, 2023, to discuss language within the label. Labeling negotiations were completed on January 30, 2023.

Please see Discipline Review Section for recommendations.

❖ REGULATORY TIMELINE & EFFICACY SUPPLEMENT DETAILS

- Pre-sNDA Meeting: November 4, 2021
- Pre-sNDA Follow-Up Meeting: December 15, 2021
- sNDA Submitted: March 31, 2022
- sNDA Received: March 31, 2022
- Filing Meeting: May 16, 2022
- Filing Date: May 30, 2022
- Filing Letter: June 9, 2022
- Team Meeting #1: June 27, 2022
- Team Meeting #2: August 3, 2022
- Midcycle Meeting: August 31, 2022
- Team Meeting #3: September 1, 2022
- Team Meeting #4: September 23, 2022
- Labeling Meeting #1: December 7, 2022
- Team Meeting #5: December 8, 2022
- Team Meeting #6: December 15, 2022
- Labeling Meeting #2: January 4, 2023
- Labeling sent to Applicant: January 6, 2023
- Team Meeting #7: January 11, 2023
- FDA & Applicant Labeling Meeting: January 18, 2023
- Labeling Meeting #3: January 26, 2023
- FDA & Applicant Labeling Meeting: January 27, 2023
- Labeling negotiations completed: January 30, 2023
- Action Date: January 31, 2023
- PDUFA Date: January 31, 2023

User Fee
Per PDUFA VI, there was no user fee associated with this efficacy supplement.

Facilities
There were no facility inspections as no new CMC information was submitted and all sites were acceptable based on previously reviewed information.

Division of Scientific Investigations
Clinical site inspections were not conducted. None of the sites enrolled more than 10% of the total population. Statistical analysis of the primary endpoint by site showed that none of the sites had an influence on the overall results.

Pediatric Review Committee (PeRC)
Sildenafil has orphan designation; therefore, the Pediatric Research Equity Act (PREA) was not triggered for this application.

Advisory Committee
Within FDA's filing letter to the Applicant, dated June 9, 2022, FDA notified the Applicant of the intent to hold an Advisory Committee (AC) meeting to provide the opportunity for public discussion of this application. An AC meeting was scheduled for December 14, 2022. A Federal Register Notice was announced for this meeting on October 6, 2022 (Docket No.: FDA-2022-N-2337). However, on October 7, 2022, FDA informed the Applicant the AC meeting was canceled indefinitely as FDA was unable to obtain the panel members with the appropriate expertise in pediatric PAH necessary to provide a productive AC meeting.

Proprietary Name
No proprietary name request was submitted as this application is an efficacy supplement.

❖ REVIEWS

❖ Primary Reviews

Divisional Concurrence, Cross Discipline Team Leader (CDTL) Review, and Clinical/Biostatistics Review (January 31, 2023)
Recommended Action: Approval
A joint collaborative review was written by the clinical and statistical teams. Dr.'s Garnett (clinical) and Bai (biostatistics) focused on efficacy and safety data. Dr. Senatore (CDTL) provided the Executive Summary within the review. Dr. Stockbridge (signatory) signed the review in concurrence.

Study No. A1481324 demonstrated a treatment effect by reducing mortality for the 20 mg and 80 mg doses compared to the 5 mg dose. Other treatment effects included a reduction in clinical worsening for the higher doses relative to the 5 mg dose, and an increase in exercise capacity for the 80 mg dose compared to the 5 mg dose.

Safety data from study No. A1481324 was based on a mean exposure of 795 days, 843 days, and 933 days for the 5, 20, and 80 mg doses, respectively. There was a linear decrease in the % subjects treated with drug over time, from 100% at month 1 to 0% at month 69. The incidence of death was highest at the lowest dose and decreased in dose-dependent manner (26%, 20%, and 15% for the 5 mg, 20 mg, and 80 mg doses, respectively).

Given these findings as well as the acceptability of PVRI as a bridging biomarker, the review team concluded that sufficient evidence was presented to warrant a recommendation to approve the 20 mg and 80 mg dose to treatment pediatric patients with PAH. Moreover, the 5 mg dose appears ineffective in attenuating adverse events associated with disease progression.

See review for full details.

Product Quality (September 26, 2022)
Recommended Action: Approval
Dr. Kalpathy provided a brief review confirming no CMC changes were proposed in this efficacy submission. The Applicant claimed S-025 qualifies for a Categorical Exclusion from the requirement to prepare an Environmental Assessment as per 21 CFR 25.31(b) because "the estimated concentration of the [drug] substance at the point of entry into the aquatic environment will be below 1 part per billion (1 µg/L)". The review stated that the Applicant's request for Categorical Exclusion is acceptable.

❖ Consult Reviews

Office of Medical Error Prevention and Risk Management, Division of Medical Error Prevention and Analysis II (dated December 8, 2022)
Dr. Mehta reviewed the PI and PPI and performed a risk assessment for areas of vulnerability with regard to medication error. She recommended to clarify each dosage form for adults and pediatrics, in addition to revising the use of error prone abbreviations/symbols. Thus, Dr. Mehta concluded labeling components can be revised to support the safe and effective use of the proposed product.

Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling Team (dated January 18, 2023)

Dr. Chung conducted a combined review with Dr. Shah to evaluate the Applicant's proposed PI, PPI, and IFU. Recommendations made to the Division included simplified wording and clarified concepts where possible. They removed unnecessary or redundant information, proposed revisions to ensure that the PPI and IFU were free of promotional language and ensured that the PPI and IFU met the criteria as specified in the guidance for industry *Useful Written Consumer Medication Information (CMI)*[1].

Office of Prescription Drug Promotion (dated January 17, 2023)

Dr. Shah conducted a review of the PI based on the draft labeling provided via email by DCN on January 6, 2023. Recommendations were made to the PI to promote the safe and effective use of the product.

❖ LABELING

Labeling discussions occurred with the Applicant. The final agreed upon labeling is attached to the Approval Letter. Major changes were updated to the PI, PPI, and IFU. Refer to attached, red-lined label for exact revisions.

❖ CONCLUSION

After taking into consideration all primary and consult reviews, the Division issued an approval letter, signed by Norman Stockbridge, Division Director for NDA 021845/S-025 on January 31, 2023.

58 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[1] https://www.fda.gov/media/72574/download

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/s/

BRIAN T COONEY
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 17, 2023
To:	Brian Cooney, MS, PSM Regulatory Health Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	REVATIO (sildenafil citrate)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 021845
Supplement Number:	S-025
Applicant:	Viatris Speciality LLC

1 INTRODUCTION

On March 31, 2022, Viatris Speciality LLC submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 021845/S-025 for REVATIO (sildenafil citrate) tablets with cross references to NDA 203109 for REVATIO (sildenafil citrate) oral suspension, NDA 022473 for REVATIO (sildenafil citrate) injection, and Investigational New Drug (IND) 064924 for REVATIO (sildenafil citrate) tablets. With this submission, the Applicant proposes a new indication (b) (4) The Applicant also proposes (b) (4) (b) (4) and provided the final study report for Study A1481324 to fulfill postmarketing study commitment 2026-1.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on December 8, 2022.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on May 26, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for REVATIO (sildenafil citrate) tablets and Instructions for Use (IFU) for REVATIO (sildenafil citrate) oral suspension.

2 MATERIAL REVIEWED

- Draft REVATIO (sildenafil citrate) tablets PPI received on March 31, 2022, and received by DMPP and OPDP on January 6, 2023.
- Draft REVATIO (sildenafil citrate) oral suspension IFU received on March 31, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 6, 2023.
- Draft REVATIO (sildenafil citrate) tablets PI received on March 31, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 6, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU documents using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
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CHARUNI P SHAH
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SHARON R MILLS
01/18/2023 01:58:30 PM

LASHAWN M GRIFFITHS
01/18/2023 02:00:11 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 17, 2023

To: Christine E Garnett., PharmD., Clinical Reviewer
Division of Cardiology and Nephrology (DCN

Brian Cooney, Regulatory Project Manager (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for
REVATIO (sildenafil) tablets, for oral use
REVATIO (sildenafil) for oral suspension
REVATIO (sildenafil) injection, for intravenous use

NDA: 021845/S-025

Background:
In response to DCN's consult request dated May 26, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Revatio (sildenafil) tablets, for oral use, oral suspension, and injection, for intravenous use. This supplement provides for a new pediatric indication within "Indications and Usage" (b) (4)

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling provided via email by DCN on January 6, 2023, and our comments are provided below.

OPDP comments on the proposed PPI and IFU will be sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240)-402-4997 or Charuni.Shah@fda.hhs.gov.

37 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

CHARUNI P SHAH
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 08, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 021845/S-025
Product Name, Dosage Form, and Strength:	Revatio (sildenafil) tablets, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Viatris
FDA Received Date:	March 31, 2022
OSE RCM #:	2022-697
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Viatris submitted a prior approval supplement for Revatio (sildenafil) tablets NDA 021845/S-025 proposing to include a pediatric indication based upon completion of postmarketing study requirement (PMR) Study A1481324. Subsequently, we reviewed the proposed Revatio Prescribing Information (PI), Patient Information, and Instructions for Use for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

Revatio (sildenafil) was approved on June 03, 2005 as 20 mg tablets under NDA 021845 for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability. On November 18, 2009 Revatio was approved as 10 mg/12.5 mL single use vials for intravenous bolus injection under NDA 022473. On August 30, 2012 Revatio was approved as a 10 mg/mL for oral suspension under NDA 203109.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Viatris submitted a prior approval supplement for Revatio tablets and cross-referencing to the NDAs for the injection and for oral suspension dosage forms. The supplement proposes a new indication (b) (4) following completion of PMR study A1481324. In addition, Viatris is proposing (b) (4)

We performed a risk assessment of the proposed PI and Patient Information Sheet for areas of vulnerability with regard to medication error. We note the need for clarity in regards to the dosage of the three dosage forms for adults and pediatrics in addition to the use of error prone abbreviations/symbols. Thus, the labeling components can be revised to support the safe and effective use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Revatio PI and Patient Information sheet can be improved to promote the safe and effective use of the product. We provide recommendations for DCN in Section 4.1 below

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Dosage and Administration Section

    a. We recommend including the dosage for adults and pediatrics in one section and not separated by dosage form.

    b. We note the use of abbreviations, e.g. TID, throughout the section for three times a day. We recommend removing abbreviations to prevent confusion and misinterpretation.

    c. As currently presented, the symbols “>” and “≤” are used to mean “greater than”, “less than” and “greater than or equal to”, respectively. We recommend removing the use of the symbols and replacing them with their intended meanings.

    d. We note very detailed instructions with images for the reconstitution of the for oral suspension dosage form. We recommend revising (b) (4) (b) (4) and streamlining the instructions to remove unnecessary information. Revise as follows:

        1. Tap the bottle to loosen the powder.
        2. Add 60 mL of water to the bottle.
        3. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds.
        4. Add another 30 mL of water to the bottle.
        5. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds.
        6. Remove cap and press the bottle adapter into the neck of the bottle. Replace the cap on the bottle.
        7. Write the expiration date of the reconstituted oral suspension on the bottle label (the expiration date of the reconstituted oral suspension is 60 days from the date of reconstitution).

2. How Supplied/Storage and Handling Section

    a. We recommend revising the storage information to replace the symbol "-" with its intended meaning "to". Revise to "Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Revatio received on March 31, 2022 from Viatris.

Table 2. Relevant Product Information for Revatio	
Initial Approval Date	June 3, 2005
Active Ingredient	sildenafil
Indication	Treatment of pulmonary arterial hypertension (WHO Group 1) in adults to improve exercise ability and delay clinical worsening [redacted (b) (4)] *(proposed)*
Route of Administration	Oral and Intravenous
Dosage Form	tablets
Strength	20 mg tablets, 10 mg/mL suspension, 10 mg/12.5 mL vials
Dose and Frequency	20 mg three times a day (oral) 10 mg three times a day (intravenous) *Proposed:* *Pediatrics greater than or equal to 20 kg: 20 mg three times a day orally* *Pediatrics less than 20 kg: 10 mg three times a day orally*
How Supplied	20 mg tablets in 90 count bottles 10 mg/12.5 mL single use vials 10 mg/mL (when reconstituted) oral suspension: [redacted (b) (4)] mL
Storage	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 7, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Revatio'. Our search identified two previous reviews[a,b], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Thomas, S. Label and Labeling Review for Revatio (NDA 203109/S-015). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 21. OSE RCM No.: 2019-1895-1.

[b] Thomas, S. Label and Labeling Review for Revatio (NDA 203109/S-015). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 31. OSE RCM No.: 2019-1895.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Revatio labels and labeling submitted by Viatris.

- Prescribing Information and Patient Information (Image not shown) received on March 31, 2022, available from \\CDSESUB1\EVSPROD\nda021845\0244\m1\us\lab-0313-20-3-lab-0575-4-2-combined-annotated.pdf

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

HINA S MEHTA
12/08/2022 10:29:35 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021845Orig1s025

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	021845 (supplement 025)
PDUFA Goal Date	January 31, 2023
OSE TTT #	2022-697
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
Associate Director for REMS	Laura Zendel, Pharm.D., BCPS
Design and Evaluation	
Review Completion Date	January 30, 2023
Subject	Evaluation of Need for a REMS
Established Name	Sildenafil
Trade Name	Revatio
Name of Applicant	Viatris Specialty, LLC
Therapeutic Class	Phosphodiesterase-5 (PDE-5) inhibitor
Formulation(s)	Oral Tablet, Powder for Oral Suspension, and Solution for Injection
Dosing Regimen	10 mg to 20 mg three times daily

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Revatio (sildenafil) is necessary to ensure the benefits outweigh its risks. Viatris Specialty, LLC submitted a supplemental New Drug Application (sNDA) 021845/S-025 for sildenafil with the proposed indication for the treatment of pulmonary arterial hypertension ([PAH]; World Health Organization [WHO] Group 1) in pediatric patients ages 1 – 17 years (b) (4) (b) (4) In 2011, an increased risk for a dose-related effect on mortality was observed in the STARTS-2 long term extension study (A1481156 [NCT00159874]) that evaluated the effectiveness of sildenafil in pediatric patients. Citing this safety concern, FDA added a new pediatric warning to the Prescribing Information in 2012 and the Post-Marketing Requirement (PMR) AFFILIATE study (A1481324 [NCT02060487]) was conducted to investigate the effects of multiple doses of sildenafil on mortality in adults with PAH. In 2020, the AFFILIATE study was stopped early according to results from the protocol-planned interim analysis demonstrating that the primary and key secondary endpoints were met. The Applicant did not submit a proposed REMS or risk management plan with this supplemental application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of sildenafil outweigh its risks. Confounding covariates impacted the ability to adequately interpret the increased risk of a dose-related effect on mortality in pediatric patients observed in the STARTS-2 study. The effectiveness of sildenafil for the treatment of PAH was demonstrated citing the totality of the efficacy data from the STARTS-1 study (A1481131 [NCT00159913]) that evaluated the effectiveness of sildenafil in pediatric patients and AFFILIATE study data using principles of pediatric extrapolation. The most commonly reported adverse events for sildenafil observed in the AFFILIATE study were consistent with established adverse events identified in previous studies conducted in subjects with PAH. Sildenafil is likely to be prescribed in a specialized setting by cardiologists and pulmonologists familiar with PAH therapy. Prescribers are expected to closely monitor patients for disease progression and response to therapy with frequent follow-up visits. The recommended dosage and administration of sildenafil will be updated and the pediatric warning for a dose-related effect on mortality will be removed to reflect results from the AFFILIATE study. The additional risks listed in the Warnings and Precautions section remain unchanged.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Revatio (sildenafil) is necessary to ensure the benefits outweigh its risks. Viatris Specialty, LLC submitted a supplemental New Drug Application (sNDA) 021845 for sildenafil with the proposed indication for the treatment of pulmonary arterial hypertension ([PAH]; World Health Organization [WHO] Group 1) in pediatric patients ages 1 – 17 years (b) (4) (b) (4) This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor proposed for the treatment of pulmonary arterial hypertension (PAH; World Health Organization [WHO] Group 1) in pediatric patients ages 1 – 17 years (b) (4) Sildenafil is currently approved for the treatment of PAH (WHO Group 1) in adults administered orally as a 5 mg or 20 mg three times daily dosing regimen. Phosphodiesterase-5 (PDE-5) is the predominant phosphodiesterase isoform in pulmonary smooth muscle cells that metabolizes cyclic guanosine monophosphate (cGMP). Inhibition of PDE-5 within pulmonary smooth muscle cells increases intracellular cGMP enhancing nitric-oxide-mediated vasodilation.[1]

Sildenafil routes of administration and formulations remain unchanged and are available as oral tablets, powder for oral suspension, and solution for injection. Duration of treatment is expected to be long term and likely administered in an outpatient setting.[a]

Sildenafil, while not a new molecular entity[b], utilized the 505(b)1 pathway and a prior approval efficacy supplement for the new proposed pediatric indication (b) (4) (b) (4) Sildenafil is currently approved for pediatric patients ages 1 – 17 years in Europe (2011), Japan (2017), and Indonesia (2019). In the United States, sildenafil is used off-label in pediatric patients for the treatment of PAH and recommended in clinical guidelines[2] despite an increased mortality warning in the label. (b) (4) (b) (4) Applicant citing an increased risk of mortality observed in the Post-Marketing Requirement (PMR) AFFILIATE study (A1481324 [NCT02060487]).

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for sNDA 021845 relevant to this review:

- 08/30/2012: FDA informed the Applicant that a PMR study was required to investigate the effects of multiple doses of sildenafil on mortality in adults with PAH
- 11/04/2021: Type B meeting held to discuss the PMR data and planned sNDA submission
- 03/31/2022: sNDA 021845 (supplement 025) received for sildenafil
- 06/09/2022: FDA informed the Applicant that an Advisory Committee meeting would be held on December 14, 2022 to discuss the available data to support a pediatric indication and results of the PMR study
- 10/20/2022: The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting was cancelled because clinical experts were not available

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Pulmonary Arterial Hypertension (PAH) is a progressive and fatal lung disease of multifactorial etiology.[3] Clinical presentation typically involves exertional dyspnea and fatigue that progresses over time until severe pulmonary hypertension (PH) with right ventricular (RV) failure develops. Increased pulmonary pressures leading to RV failure is the major cause of death in this rare disease.[c] Surveillance data in the United States suggests increased mortality associated with PH in men, women, and all race and ethnic groups.[4] The 7-year survival rate in adults is about 49%.[5] Pediatric PAH shares common features of adult disease but is associated with several additional disorders and challenges that require unique approaches. Children have a greater predominance of idiopathic pulmonary arterial hypertension (IPAH), PAH associated with congenital heart disease (PAH-CHD), and developmental lung diseases.[6] Disease progression also appears to be more rapid in children compared to adults. According to a United Kingdom cohort study, the incidence and prevalence ranges from 0.5 to 1 case per million and 2.1 cases per million children, respectively.[7,d]

3.2 Description of Current Treatment Options

Initial screening of pediatric PH patients involves a comprehensive history and physical examination, combined with diagnostic testing for the assessment of PH pathogenesis and classification, and formal assessment of cardiac function.[2] Treatment of PH in pediatric patients generally relies on small observational studies and evidence-based data extrapolated from adult patient populations. The CRDAC determined hemodynamic measurements (Pulmonary Vascular Resistance Index [PVRI] or Mean Pulmonary Arterials Pressure [mPAP]) could be used to demonstrate effectiveness and derive dosing information in pediatric patients with PAH for treatment options with an approved indication in adult patients with PAH.[8] Currently, bosentan is the only FDA-approved treatment option indicated for PAH (WHO Group 1) in pediatric patients ≥ 3 years with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), resulting in an improvement in exercise ability. Off-label targeted treatment options recommended in treatment guidelines[2] include prostacyclin derivatives, endothelin receptor antagonists (ERA), and phosphodiesterase-5 (PDE-5) inhibitors (Table 1).

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: Targeted Treatment Options for Pediatric Pulmonary Hypertension

Product Trade Name (Generic)	Pediatric Off-Label Use	ROA	REMS (Boxed Warning)	Warnings and Precautions
Prostacyclin Derivatives				
Flolan, Veletri (epoprostenol)	Yes	IV	No	Rebound PH following Abrupt Withdrawal, Hypotension, Bleeding, PVOD
Ventavis (iloprost)	Yes	INH		Syncope, PVOD, Bronchospasm, Avoid Contact with Skin and Eyes, and Ingestion
Orenitram, Remodulin, Tyvaso, Tyvaso DPI (treprostinil)	Yes	Oral, IV, SubQ, INH		Hypotension, Bleeding, Rebound PAH following Abrupt Withdrawal
Endothelin Receptor Antagonists				
Letairis (ambrisentan)	Yes	Oral	Yes (Embryo-Fetal Toxicity)	Fluid Retention, Hemoglobin and Hematocrit Decrease, PVOD, Decreased Sperm Counts
Tracleer (bosentan)	FDA Approved		Yes (Embryo-Fetal Toxicity and Hepatotoxicity)	Fluid Retention, Hemoglobin and Hematocrit Decrease, PVOD, Decreased Sperm Counts
Phosphodiesterase-5 (PDE-5) Inhibitors				
Revatio (sildenafil)	Yes	Oral, IV	No	Mortality with Pediatric Use, Epistaxis, Vaso-Occlusive Crisis, Hypotension, PVOD, Visual Loss, Hearing Impairment, Priapism
Adcirca (tadalafil)	Yes	Oral		Hypotension, PVOD, Visual Loss, Hearing Impairment, Priapism

No safety issues warranting a REMS have been identified for current FDA-approved prostacyclin derivatives or PDE-5 inhibitors. All ERAs require a REMS with elements to assure safe use (ETASU) to ensure the benefits outweigh the risk of embryo-fetal toxicity. The bosentan REMS also addresses the risk of hepatotoxicity. In general, the warnings and precautions for prostacyclin derivatives are similar, as are the warnings and precautions for PDE-5 inhibitors. Pulmonary Veno-Occlusive Disease (PVOD) has been identified in all classes of currently FDA-approved treatment options for PH despite similar signs and symptoms of PVOD and progressive PH. Various routes of administration (ROA) for treatment options are available. Modest changes in mortality rates, progressive clinical manifestations of PH, and only one other FDA-approved targeted treatment option in pediatric patients represent an unmet medical need.

4 Benefit Assessment

The efficacy of sildenafil for the treatment of PAH (WHO Group 1) in pediatric patients ages 1 – 17 years was extrapolated from the AFFILIATE study conducted to investigate the effects of multiple doses of sildenafil on mortality in adults with PAH. The AFFILIATE study was a randomized, double-blind, parallel-group study that represented a total of 385 subjects randomized to treatment with sildenafil when administered at three doses (5 mg, 20 mg, or 80 mg, all three times daily). Subjects from 63 active sites in 23 countries were ≥ 18 years of age enrolled with any of the following conditions:

- Idiopathic Primary Pulmonary Arterial Hypertension (IPAH)
- PAH secondary to connective tissue disease
- PAH with surgical repair (at least 5 years previously) of atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA) and aorto-pulmonary window
- PAH diagnosis confirmed by right heart catheterization occurring ≤ 1 year prior to randomization
- Functional Class II-IV; Baseline 6-Minute Walk Distance (6MWD) ≥ 50 meters

Subjects were excluded from the study with any of the following conditions:

- Significant (> 2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation
- History of cardiac arrest, respiratory arrest, hemodynamic collapse, CPR, ventricular tachycardia, ventricular fibrillation, or uncontrolled atrial fibrillation
- History of pulmonary embolism; History of chronic lung disease / restrictive lung disease (e.g., chronic obstructive pulmonary disease (COPD) or scleroderma) with impairment of lung function
- No prior long term treatment with PDE-5 inhibitors
- Treatment with bosentan OR riociguat within 3 months of randomization
- Current treatment with nitrates or nitric oxide

The study was stopped early citing results from the protocol-planned interim analysis demonstrating that the primary endpoint was met; a non-inferiority analysis that the mortality rate of the 80 mg dose was no worse than double the mortality rate of the 5 mg dose. Hazard ratios (HR) regarding overall survival are summarized in Table 2.

Table 2: Hazard Ratios for Overall Survival From the AFFILIATE Study

Sildenafil Dose	Subject-Years of Follow-Up	Deaths	On-Treatment Deaths	Off-Treatment Deaths	HR Compared to 5 mg	HR Compared to 20 mg
		n (%) Subjects			(99.7% CI)	
5 mg (N = 129)	329.8	34 (26.4%)	22 (17.1%)	12 (9.3%)		
20 mg (N = 128)	340.5	24 (19.5%)	13 (10.2%)	12 (9.4%)	0.68 [p = 0.14] (0.31 – 1.49)	
80 mg (N = 128)	356.7	19 (14.8%)	15 (11.7%)	4 (3.1%)	**0.51 [p = 0.02] (0.22 – 1.21)**	0.74 [p = 0.33] (0.30 – 1.84)

Source: Adapted from statistical reviewer's analysis

The Applicant concluded data from the STARTS-1 study demonstrating an improvement in exercise capacity and decreased PVRI, and extrapolated data from adult subjects in the AFFILIATE study demonstrating reduced mortality for the 20 mg and 80 mg dose regimen compared to the 5 mg dose regimen, supports the use of sildenafil in pediatric patients with PAH [(b) (4)] [(b) (4)] The clinical reviewers concluded sufficient evidence was presented to warrant approval of the 20 mg and 80 mg dose regimen of sildenafil for the treatment of PAH (WHO Group 1) in pediatric patients ages 1 – 17 years [(b) (4)] [(b) (4)] This determination relied on the acceptability of PVRI as a bridging biomarker to demonstrate effectiveness and derive dosing information in pediatric patients with PAH, a demonstrated treatment effect by reducing clinical worsening and mortality for the 20 mg and 80 mg dose regimen compared to the 5 mg dose regimen, and an increase in exercise capacity for the 80 mg dose regimen compared to the 5 mg dose regimen.

5 Risk Assessment & Safe-Use Conditions

The safety of sildenafil for the treatment of PAH (WHO Group 1) in pediatric patients ages 1 – 17 years relied on data from the AFFILIATE study. Additional safety analysis relied on post-marketing safety data and the STARTS-1 and STARTS-2 studies. The safety analysis of data from the AFFILIATE study compared death, serious adverse events (SAEs), and treatment emergent adverse events (TEAEs) that occurred in the 5 mg dose group to the 20 mg and 80 mg dose groups. While the non-inferiority criteria of the AFFILIATE study were met, the highest number of observed deaths, SAEs, and severe TEAEs occurred in the 5 mg dose group compared to the 20 mg and 80 mg dose groups. The safety concern of increased mortality risk related to the 5 mg dose was cited (b) (4) (b) (4) Treatment emergent adverse events (TEAE) and mortality data are summarized in Table 3.

Table 3: Treatment Emergent Adverse Events From the AFFILIATE Study

Adverse Event (AE) Category	Sildenafil 5 mg (N = 129)	Sildenafil 20 mg (N = 128)	Sildenafil 80 mg (N = 128)
	n (%) Subjects		
Deaths	34 (26.4%)	24 (19.5%)	19 (14.8%)
Serious AE	66 (51.2%)	49 (38.3%)	51 (39.8%)
Any AE Leading to Permanent Discontinuation	15 (11.6%)	13 (10.2%)	20 (15.6%)
Any AE Leading to Dose Modification of Sildenafil	14 (10.9%)	13 (10.2%)	21 (16.4%)
Any AE Leading to Interruption of Sildenafil	14 (10.9%)	12 (9.4%)	21 (16.4%)
Any AE Leading to Dose Reduction of Sildenafil	0	1 (0.8%)	0
Any TEAE	113 (87.6%)	113 (88.3%)	116 (90.6%)
Severe	58 (45%)	41 (32%)	39 (30.5%)
Moderate	79 (61.2%)	67 (52.3%)	75 (58.6%)
Mild	98 (76%)	96 (75%)	100 (78.1%)

Source: Clinical reviewer's analysis

The most commonly reported on-treatment adjudicated cause of death was PAH and occurred at a higher rate in the 5 mg (8.5% [11/129]) dose group compared to the 20 mg (3.9% [5/128]) and 80 mg (5.5% [7/128]) dose groups. Disease-specific SAEs (pulmonary hypertension and cardiac failure) were more frequently reported in the 5 mg (22.5% [29/129] and 17.8% [23/129]) dose group compared to the 20 mg (14.8% [19/128] and 10.2% [13/129]) and 80 mg (10.9% [14/128] and 8.6% [11/129]) dose groups. The majority of TEAE were classified as mild or moderate, however a higher risk for severe TEAEs (incidence ≥ 2%) of severe PAH, right heart failure, and sudden death were detected in the 5 mg dose group. Severe diarrhea events occurred at a higher rate in the 80 mg dose group.

The review team evaluated post-marketing safety data and the final dataset from the STARTS-2 study. No new safety information was identified by the clinical reviewer in a review of serious AEs from the post-marketing safety database and mortality events were determined to be consistent with progression of PAH disease and heart failure. Furthermore, the review team concluded confounding covariates impacted the ability to adequately interpret the increased risk of a dose-related effect on

mortality in pediatric patients observed in the STARTS-2 study. This determination relied on a demonstrated treatment effect by reducing clinical worsening and mortality observed in the AFFILIATE study.

6 Expected Postmarket Use

Sildenafil is likely to be prescribed in an outpatient setting by cardiologists and pulmonologists familiar with pediatric PAH therapy. The likely prescribers are expected to be familiar with predicted risks of PDE-5 inhibitor therapy and closely monitor patients for disease progression and response to therapy with frequent follow-up visits for this rare disease.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sildenafil beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of sildenafil for the treatment of PAH (WHO Group 1) in pediatric patients ages 1 – 17 years citing the totality of the efficacy data from the STARTS-1 study that evaluated the effectiveness of sildenafil in pediatric patients and extrapolated data from adult subjects in the AFFILIATE study demonstrating reduced mortality for the 20 mg and 80 mg dose regimen compared to the 5 mg dose regimen, the seriousness of PH, and an adequately favorable benefit-risk profile.

In 2011, an increased risk for a dose-related effect on mortality was observed in the STARTS-2 study that evaluated the effectiveness of sildenafil in pediatric patients. Citing this safety concern, FDA added a pediatric warning describing the increased risk for a dose-related effect on mortality to the Prescribing Information in 2012 and the Post-Marketing Requirement AFFILIATE study was conducted to investigate the effects of multiple doses of sildenafil on mortality in adults with PAH. In 2020, the AFFILIATE study was stopped early according to results from the protocol-planned interim analysis demonstrating that the primary and key secondary endpoints were met. A planned Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting scheduled on December 14, 2022 to discuss the results of the AFFILIATE study in adult patients with PAH and whether the results could be extrapolated to support the indication for sildenafil for the treatment of PAH (WHO Group 1) in pediatric patients ages 1 – 17 years was cancelled on October 20, 2022 because clinical experts were not available.

The previous Agency decision to use hemodynamic measurements to demonstrate effectiveness and derive dosing information in pediatric patients with PAH for treatment options with an approved indication in adult patients with PAH[8] was cited to interpret and extrapolate the results of the AFFILIATE study to the pediatric population. A demonstrated treatment effect by reducing clinical worsening and mortality for the 20 mg and 80 mg dose regimen compared to the 5 mg dose regimen, and an increase in exercise capacity for the 80 mg dose regimen compared to the 5 mg dose regimen supported the indication for sildenafil for the treatment of PAH (WHO Group 1) in pediatric patients ages 1 – 17 years.

Data from the AFFILIATE study put into question the previous finding of the increased risk of a dose-related effect on mortality in pediatric patients observed in the STARTS-2 study. In addition, no new

safety information was identified by the clinical reviewer in a review of serious AEs from the post-marketing safety database and mortality events were determined to be consistent with progression of PAH disease and heart failure. The safety concern of increased mortality risk related to the 5 mg dose was cited (b) (4) (b) (4) The pediatric warning for a dose-related effect on mortality will be removed to reflect results from the AFFILIATE study. The additional risks listed in the Warnings and Precautions section remain unchanged.

In general, healthcare providers who treat PH should be familiar with predicted risks of PDE-5 inhibitor therapy and closely monitor patients for disease progression and response to therapy with frequent follow-up visits for this rare disease. Relying on the therapeutic benefit observed in the AFFILATE study, lack of new safety information from post-marketing safety data, and uncertainty of the dose-related effect on mortality observed in the STARTS-2 study, a REMS is not necessary to ensure that the benefits outweigh the risks for sildenafil for the intended population. Therefore, this reviewer is not recommending a REMS for the management of the risks of sildenafil therapy.

9 Conclusion & Recommendations

Relying on the data available, a REMS is not necessary to ensure the benefits of sildenafil outweigh the increased risk of a dose-related effect on mortality in pediatric patients with PAH observed in the STARTS-2 study. The benefits of sildenafil were demonstrated citing the totality of the efficacy data from the STARTS-1 study that evaluated the effectiveness of sildenafil in pediatric patients and extrapolated data from adult subjects in the AFFILIATE study demonstrating reduced mortality for the 20 mg and 80 mg dose regimen compared to the 5 mg dose regimen. Safety concerns observed in the AFFILIATE study were consistent with established adverse events identified in previous studies conducted in subjects with PAH. Healthcare providers who treat PAH should be familiar with monitoring and treating predicted risks of PDE-5 inhibitor therapy. At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

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