



NDA 021845/S-012; S-013  
NDA 022473/S-005; S-006  
NDA 203109/S-003; S-004

**SUPPLEMENT APPROVAL**

Pfizer, Inc.  
Attention: Christine Kobryn, Ph.D.  
Associate Director, Worldwide Regulatory Strategy  
235 East 42<sup>nd</sup> Street  
New York, NY 10017-5755

Dear Dr. Kobryn:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 31, 2013 for supplements NDA 021845/S-012, NDA 022473/S005 and S-006, and NDA 203109/S-003 and S-004, and dated August 1, 2013 for NDA 021845/S-013, received August 1, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Revatio 20 mg Tablets (NDA 021845), Revatio 10 mg/12.5 mL for Injection (NDA 022473), and Revatio 10 mg/mL Powder for Oral suspension (NDA 203109).

We acknowledge receipt of your amendments dated August 21, September 19, October 18, and November 1, 15, and 22, 2013.

These “Changes Being Effected” supplemental new drug applications provide for the addition of a 5 mg dosage form and the following labeling revisions:

- 1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following test was added/deleted:

<u>INDICATIONS AND USAGE (1)</u>	<u>01/2014</u>
<u>DOSAGE AND ADMINISTRATION, REVATIO Tablets and Oral Suspension (2.1)</u>	<u>01/2014</u>
<u>DOSAGE AND ADMINISTRATION, REVATIO Injection (2.2)</u>	<u>01/2014</u>
<u>DOSAGE AND ADMINISTRATION, Reconstitution of the Powder for Oral Suspension (2.3)</u>	<u>01/2014</u>
<u>Contraindications (4)</u>	<u>08/2012</u>
<u>Warnings and Precautions (5)</u>	<u>08/2012</u>
<u>Warnings and Precautions (5.2)</u>	<u>08/2012</u>
<u>Warnings and Precautions (5.10)</u>	<u>07/2013</u>

- 2. In **HIGHLIGHTS/INDICATIONS AND USAGE**, the following text was added/deleted:

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity. The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.-(1, 14)

3. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following text was deleted:

- Tablet and oral suspension: 5 mg or 20 mg three times a day, 4-6 hours apart (b) (4)  
(2.1)
- Injection: 2.5 mg or 10 mg (~~12.5 mL~~) three times a day administered as an intravenous bolus injection (2.2)

4. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the sixth bullet was deleted:

(b) (4)

5. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was deleted:

(b) (4)

6. Under **INDICATIONS AND USAGE**, the following text was added/deleted:

**Limitation of Use:** Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity [see Clinical Studies (14)].

**Limitation of Use**

The efficacy of REVATIO in the treatment of pulmonary arterial hypertension (PAH) has not been adequately evaluated in patients taking bosentan.

7. Under **DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

**2.1 REVATIO Tablets and Oral Suspension**

The recommended dose of REVATIO is 5 mg or 20 mg three times a day (~~TID~~). Administer REVATIO doses 4-6 hours apart ~~during waking hours~~.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg ~~TID~~ three times a day is not recommended.

**2.2 REVATIO Injection**

REVATIO injection is for the continued treatment of patients with PAH who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.

The recommended dose of REVATIO is 2.5 mg or 10 mg administered as an intravenous bolus injection three times a day (~~TID~~). The dose of REVATIO injection does not need to be adjusted for body weight.

8. Under **DOSAGE FORMS AND STRENGTHS**, the following text was added/deleted:

**REVATIO Tablets**

~~REVATIO tablets are supplied as white~~ White, film-coated, round tablets engraved with “RVT20” containing sildenafil citrate equivalent to 20 mg of sildenafil.

**REVATIO Injection**

~~REVATIO injection is supplied as a~~ Single use vial containing 10 mg/12.5 mL of sildenafil.

**REVATIO for Oral Suspension**

~~REVATIO for oral suspension is supplied in 125 mL bottles. Bottles containing 32.27 g of a~~ White to off-white powders containing 1.57 g of sildenafil citrate (equivalent to 1.12 g of sildenafil) in a bottle intended for constitution. (b) (4)

~~Following constitution with 90 mL of water, the volume of the oral suspension is 112 mL and the oral suspension contains 10 mg/mL sildenafil. Each bottle contains 1.57 g of sildenafil citrate (1.12 g sildenafil).~~ A 2 mL oral syringe (with 0.5 mL and 2 mL dose markings) and a press-in bottle adaptor are also provided.

9. Under **WARNINGS AND PRECAUTIONS**, the following section was deleted:



10. Under **USE IN SPECIFIC POPULATIONS, Pregnancy**, the following text was deleted from the end of the section:

**Pregnancy Category B**

~~There are no adequate and well-controlled studies of sildenafil in pregnant women. 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<sup>2</sup> basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg ~~TD~~ 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<sup>2</sup> basis). ~~Because animal reproduction studies are not always predictive of human response, REVATIO should be used during pregnancy only if clearly needed.~~~~

11. Under **DESCRIPTION**, the following text was added/deleted:

REVATIO (sildenafil) Tablets: REVATIO is formulated as white, film-coated round tablets with 20 mg of sildenafil 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: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, 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 to 1.12 g sildenafil) in an amber glass bottle intended for constitution as a white to off-white powder providing a white to off-white grape flavored oral suspension when constituted. Bottles containing 32.27 g powder for oral suspension are intended for following constitution with 90 mL water, the volume of the oral suspension is 112 mL and the oral suspension contains 10 mg/mL sildenafil to produce an oral suspension containing 10 mg/mL sildenafil. 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. The inactive ingredients include sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide, sodium benzoate, colloidal silicon dioxide anhydrous and grape flavor. 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. Under **CLINICAL PHARMACOLOGY, Pharmacokinetics**, the following text was added:

**Effects of REVATIO on Hemodynamic Measures**

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 [Study 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 3. The relationship between these effects and improvements in 6-minute walk distance is unknown.

**Table 3. Changes from Baseline in Hemodynamic Parameters at Week 12 [mean (95% CI)] for the REVATIO 20 mg Three Times a Day and Placebo Group**

	<b><u>Placebo (n = 65)*</u></b>	<b><u>REVATIO 20 mg three times a day (n = 65)*</u></b>
<b><u>mPAP (mmHg)</u></b>	0.6 (-0.8, 2.0)	-2.1 (-4.3, 0.0)
<b><u>PVR (dyn·s/cm<sup>5</sup>)</u></b>	49 (-54, 153)	-122 (-217, -27)
<b><u>SVR (dyn·s/cm<sup>5</sup>)</u></b>	-78 (-197, 41)	-167 (-307, -26)

<b><u>RAP (mmHg)</u></b>	<u>0.3 (-0.9, 1.5)</u>	<u>-0.8 (-1.9, 0.3)</u>
<b><u>CO (L/min)</u></b>	<u>-0.1 (-0.4, 0.2)</u>	<u>0.4 (0.1, 0.7)</u>
<b><u>HR (beats/min)</u></b>	<u>-1.3 (-4.1, 1.4)</u>	<u>-3.7 (-5.9, -1.4)</u>

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.

In another study evaluating lower doses of sildenafil 1 mg, 5 mg and 20 mg [Study 3 in Clinical Studies (14)], there were no significant differences in the effects on hemodynamic variables between doses.

13. Under **CLINICAL PHARMACOLOGY, Pharmacokinetics**, the following text was added/deleted:

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 higher at a dose of 80 mg TID compared to its the exposure at a dose of 20 mg three times a day TID. 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 potent 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., which is consistent with the effect of bosentan on sildenafil clearance in healthy volunteers. Concomitant administration of potent CYP3A inducers is expected to cause substantial decreases in plasma levels of sildenafil.

(b) (4)

(b) (4)

### Epoprostenol

The mean reduction of sildenafil (80 mg TID ~~three times a day~~) bioavailability ~~due to when co-administration 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.

14. Under **CLINICAL PHARMACOLOGY**, the following text was added/deleted from the footnotes under Figure "8" and "9":

\*\*\*No ~~(b) (4)~~ benefit in exercise capacity when sildenafil added to bosentan therapy [see *Clinical Studies (14)*]

15. Under **CLINICAL STUDIES**, the following text was added/deleted:

### **Studies of Adults with Pulmonary Arterial Hypertension**

#### **Study 1 ~~(b) (4)~~ sREVATIO monotherapy (20 mg, 40 mg, and 80 mg three times a day)**

Patients on all REVATIO doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo. Data from other hemodynamic parameters for the REVATIO 20 mg TID three times a day and placebo dosing regimens is displayed in Table 3. The relationship between these effects and improvements in 6 minute walk distance is unknown.

**Table 3. Changes from Baseline in Hemodynamic Parameters at Week 12 [mean (95% CI)] for the REVATIO 20 mg TID Three Times a Day and Placebo Group**

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

**Study 2 (REVATIO co-administered with epoprostenol- (b) (4))**

**Study 3 (REVATIO monotherapy (1 mg, 5 mg, and 20 mg three times a day) (b) (4))**

A randomized, double-blind, parallel dose study (Study 3) was planned in 219 patients with PAH. This study was prematurely terminated (b) (4)

with 129 subjects enrolled. (b) (4)

Patients were required to have a mPAP greater than or equal to 25 mmHg and a PCWP less than or equal to 15 mmHg at rest via right heart catheterization within 12 weeks 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 345 meters). Patients were randomized to 1 of 3 doses of REVATIO: 1 mg, 5 mg, and 20 mg, three times a day.

(b) (4)  
At baseline patients had PPH (74%) or secondary PAH (26%); WHO functional class II (57%), III (41%), or IV (2%); the mean age was 44 years; and 67% were female. The majority of subjects were Asian (67%), and 28% were Caucasian.

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. Similar increases in walk distance (mean increase of 38-41 meters) were observed in the 5 and 20 mg dose groups. These increases were significantly better than those observed in the 1 mg dose group (Figure 12).

**Figure 12. Mean Change from Baseline in Six Minute Walk (meters) by Visit to Week 12 – ITT Population**  
**Sildenafil Protocol A1481244**

**Study 4 (b) (4) -REVATIO added to (b) (4) 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 three 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 (62.5-125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 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 .



16. Under **HOW SUPPLIED/STORAGE AND HANDLING**, the following text was added/deleted:

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 - 25°C (68°F - 77°F) ; excursions permitted to 15°C - 30°C (59°F - 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 - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

REVATIO powder for oral suspension is supplied in ~~125 mL~~ amber glass bottles. Each bottle contains white to off-white powders containing 1.57 g of sildenafil citrate (equivalent to 1.12 g sildenafil)~~32.27 g of powder for oral suspension~~. Following constitution, the 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. ~~The shelf life of the powder for oral suspension is 24 months.~~

#### Constituted Oral Suspension

Store below 30°C (86°F) or in refrigerator at 2°C to 8°C (36° F - 46°F). Do not freeze. The shelf-life of the constituted oral suspension is ~~30~~60 days. Any remaining oral suspension should be discarded ~~30~~60 days after constitution.

17. There are editorial changes noted throughout the label (i.e. the abbreviation TID was changed to read three times a day).

18. The revision date and version number were updated.

#### **The following changes were made to the Patient Package Insert:**

19. Under **What is REVATIO?**, the following text was added/deleted:

- REVATIO is not for use in children
- ~~Adding~~It is not known if REVATIO to another medication used to treat is effective for the treatment of PAH, bosentan (Tracleer®), does not result in <sup>(b)(4)</sup>-added improvement in your ability to exercise- <sup>(b)(4)</sup>. in people who are also taking a medicine called bosentan (Tracleer®)

20. Under **How should I store REVATIO?**, the following text was added/deleted from the fourth bullet:

- Throw away REVATIO oral suspension after ~~30~~60 days.

21. The revision date and version number were updated.

There are no other changes from the last approved package insert.

#### **APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

#### **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(1)] in structured product labeling (SPL) format using the FDA automated drug

registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), 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 titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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(1)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), 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 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

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

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If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC  
Regulatory Project Manager for Safety  
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, PharmD.  
Deputy Director for Safety  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
01/31/2014