



IMPORTANT DRUG WARNING

Pfizer Inc

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New York, NY 10017

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Dear Health Care Professional:

Pfizer is writing to inform you of important safety information from a clinical trial regarding REVATIO® (sildenafil) tablets for the treatment of pulmonary arterial hypertension (PAH) in pediatric patients. You are being sent this communication because you may be involved in the care of pediatric PAH patients.

Indication:

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

PLEASE NOTE THAT REVATIO IS NOT APPROVED FOR USE IN PEDIATRIC PATIENTS.

In an ongoing long-term extension study of REVATIO for the treatment of PAH in pediatric patients (Study A1481156) with doses in the range of 10-80 mg three times a day (TID), a higher risk of mortality was observed among patients in the higher compared to lower study-specific dose groups. Study A1481156, the long-term, open-label extension to the REVATIO pediatric pivotal trial (A1481131) has been ongoing since 2003. In the double-blind, placebo-controlled pivotal trial, pediatric patients with PAH were randomized to low-, medium-, or high-dose sildenafil or placebo for 16 weeks of treatment. Following completion of this treatment period, patients were eligible to enter the long-term extension study. Patients entering the extension study who received active treatment during the 16-week pivotal trial continued the same dosing regimen as assigned during the pivotal trial; patients who received placebo in the 16-week trial were randomized to low-, medium-, or high-dose groups upon entry into the extension study. Both upward and downward dose titration of sildenafil were permitted throughout the course of the long-term extension study.

The doses corresponding to the low-, medium-, and high-dose groups for each of the three weight categories in the pivotal and extension studies are presented in the following table (doses were administered TID):

Body Weight (kg)	Low Dose	Medium Dose	High Dose
≥8-20	NA	10 mg	20 mg
>20-45	10 mg	20 mg	40 mg
>45	10 mg	40 mg	80 mg

Please see Important Prescribing Information enclosed.

An independent Data Monitoring Committee (DMC) has been following mortality trends across the 3 dose groups since the completion of the pivotal trial in 2008. The DMC is chartered to meet either annually or after a further 5 deaths since the last DMC, whichever is sooner. The DMC met on 26th July 2011 to review the data from a recent data cut in which there were 4 newly reported deaths since the previous DMC meeting in November 2010. At the time of the review, all subjects were at least 3 years post randomization (some as long as approximately 7 years) and a total of 35 deaths had been reported either on treatment or during the survival follow-up after discontinuation from the study. Of the 35 deaths reported in Study A1481156, 5 were in the low groups (5/55; 9%), 10 in the medium groups (10/74; 14%) and 20 in the high-dose groups (20/100; 20%). Most deaths were assessed by the investigator as associated with disease progression and none were assessed as causally related to study treatment. The Kaplan-Meier survival estimates within dose groups at 3 years were 94%, 93% and 89% for the low-, medium-, and high-dose groups, respectively.

Based on these data, the DMC unanimously concluded that, in the context of this clinical trial, the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose. The DMC also expressed concern as to the potential dose-response relationship between increasing dose and mortality. Therefore, the DMC recommended immediate discontinuation of the 40 and 80 mg TID doses, as well as of the 20 mg TID dose in children with body weight \leq 20 kg. The DMC emphasized that these recommendations should not be extrapolated to the use of REVATIO® (sildenafil) in adults.

Pfizer has taken immediate steps to inform the study investigators and the FDA of the DMC recommendations and has implemented the recommended changes to the ongoing study.

To report an adverse event, or for more information, please direct all of your medically related questions about REVATIO to U.S. Medical Information at 1-800-438-1985.

Regards,

Ivan Levinson

Ivan Levinson, MD
Vice President
North American Medical Affairs
Pfizer Inc

Please see Important Prescribing Information enclosed.

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, REVATIO (sildenafil) injection
Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2010
Warnings and Precautions (5.8)	11/2010
Dosage and Administration (2)	11/2009

INDICATIONS AND USAGE

REVATIO is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

Limitation of use: The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently. (1)

DOSAGE AND ADMINISTRATION

- Tablets: 20 mg three times a day, approximately 4-6 hours apart, with or without food. (2.1). Higher doses not recommended. (2.1)
- Injection: 10 mg (12.5 mL) three times a day administered as an IV bolus injection. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 20 mg (3)
- Injection: 10 mg (12.5 mL) single use vial. (3)

CONTRAINDICATIONS

- Use with organic nitrates. (4.1)
- History of hypersensitivity reaction to sildenafil or any component of the tablet. (4.2)

WARNINGS AND PRECAUTIONS

- Cardiovascular effects: Carefully consider whether patients with certain underlying conditions (e.g., resting hypotension, fluid

depletion) could be adversely affected by vasodilatory effects of REVATIO. Not recommended in patients with pulmonary veno-occlusive disease. (5.1)

- Use with alpha-blockers: Note additive blood pressure-lowering effects. (5.1)
- Bleeding: In patients with PAH secondary to CTD, higher rates of epistaxis with REVATIO than placebo, including with concomitant oral vitamin K antagonists. (5.2)
- Use with ritonavir and other potent CYP3A inhibitors: Coadministration not recommended. (5.3)
- Effects on the eye: Consider discontinuing REVATIO if sudden loss of vision occurs, which could be non-arteritic ischemic optic neuropathy (NAION). (5.4)
- Hearing impairment: Discontinue REVATIO if sudden decrease or loss of hearing occurs. (5.5)
- Use with PDE5 inhibitors: Avoid use with VIAGRA or other PDE5 inhibitors. (5.6)
- Prolonged erection: Advise patients to seek emergency treatment if an erection lasts > 4 hours. Use REVATIO with caution in patients predisposed to priapism. (5.7)
- Pulmonary hypertension secondary to sickle cell disease: REVATIO may cause serious vaso-occlusive crises. (5.8)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 3\%$ and more frequent than placebo) include epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Renal Impairment: No dose adjustments required (including severe impairment CL_{cr} < 30 mL/min). (12.3)
- Hepatic Impairment: Mild to moderate require no dose adjustment. Severe has not been studied. (12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2010

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Full Prescribing Information

1 INDICATIONS AND USAGE

REVATIO® is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

Limitation of Use

The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

2 DOSAGE AND ADMINISTRATION

2.1 Pulmonary Arterial Hypertension (PAH)

REVATIO Tablets

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

REVATIO Injection

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

The recommended dose is 10 mg (corresponding to 12.5 mL) 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.

3 DOSAGE FORMS AND STRENGTHS

REVATIO Tablets

REVATIO tablets are supplied as 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.

4 CONTRAINDICATIONS

4.1 Use with Organic Nitrates

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

4.2 Hypersensitivity Reactions

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet or injection.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reaction. The majority of reported events were non-serious hypersensitivity reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Effects

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 with resting hypotension [BP < 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction).

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.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution for:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP > 170/110);
- Patients currently on bosentan therapy.

Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported [see *Drug Interactions (7)*]. No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

5.2 Effects on Bleeding

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-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.

5.3 Use with Ritonavir and Other Potent CYP3A Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A inhibitors with REVATIO is not recommended [see *Drug Interactions (7)* and *Clinical Pharmacology (12.3)*].

5.4 Effects on the Eye

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors [see *Adverse Reactions (6.2)*].

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

5.5 Hearing Impairment

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [see *Adverse Reactions (6.2)*].

5.6 Combination with other PDE5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

5.7 Prolonged Erection

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 Pulmonary Hypertension Secondary to Sickle Cell Anemia

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 of REVATIO in PH secondary to sickle cell anemia has not been established.

6 ADVERSE REACTIONS

The following serious adverse reactions 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 [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.

Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent (> 1%) than Placebo

ADVERSE EVENT %	Placebo (n = 70)	REVATIO 20 mg TID (n = 69)	Placebo-Subtracted
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis nos	0	4	4
Diarrhea nos	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis nos	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

nos: Not otherwise specified

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinting to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (> 6% difference) are shown in Table 2.

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo

ADVERSE EVENT %	Placebo + Epoprostenol (n = 131)	REVATIO + Epoprostenol (n = 134)	Placebo-Subtracted %
Headache	34	57	23
Edema [^]	13	25	14
Dyspepsia	2	16	14
Pain in extremity	6	17	11
Diarrhea	18	25	7
Nausea	18	25	7
Nasal congestion	2	9	7

[^]includes peripheral edema

REVATIO Injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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.

Decreases in and Loss of Vision

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 postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [see *Warnings and Precautions* (5.4)].

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. 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 [see *Warnings and Precautions* (5.5)].

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

7 DRUG INTERACTIONS

Nitrates

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

Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended [see *Warnings and Precautions* (5.3)].

Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see *Warnings and Precautions* (5.1)].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine

When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. 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/m² basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, REVATIO should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

The safety and efficacy of Revatio during labor and delivery has not been studied.

8.3 Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

8.5 Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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 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 Renal Impairment

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

10 OVERDOSAGE

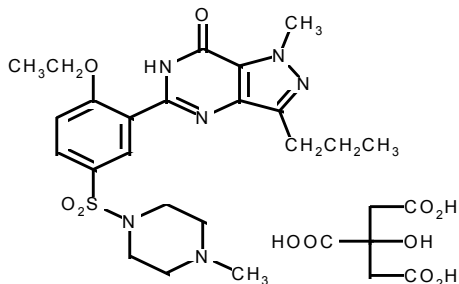
In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

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, a therapy for pulmonary arterial hypertension, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5). 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-1H-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 Tablets: REVATIO is formulated as white, film-coated round tablets equivalent to 20 mg of sildenafil for oral administration. 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 Injection: REVATIO is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg (12.5 mL) of sildenafil. Each mL of solution contains 1.124 mg sildenafil citrate, 50.5 mg dextrose and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilation 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, > 80-fold for PDE1, > 700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold 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 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 ECG. After chronic dosing of 80 mg TID to patients with pulmonary arterial hypertension, no clinically relevant effects on ECG were reported.

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

After chronic dosing of 80 mg TID sildenafil to patients with pulmonary arterial hypertension, 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% (25-63%). 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 (V_{ss}) 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.

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 PDE5 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 pulmonary arterial hypertension, 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 20-50% 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 pulmonary hypertension compared to healthy volunteers.

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 (18-45 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 ($CL_{cr} = 50-80$ mL/min) and moderate ($CL_{cr} = 30-49$ mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe ($CL_{cr} < 30$ 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 subjects with severe renal impairment compared to subjects 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

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 ($IC_{50} > 150$ μ M).

Ritonavir and other CYP3A Inhibitors

In study in healthy volunteers, co-administration with ritonavir, a potent CYP3A inhibitor, at steady state (500 mg BID) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Although the interaction between other protease inhibitors (except saquinavir) and REVATIO has not been studied, their concomitant use is expected to increase sildenafil levels.

Population data from patients in clinical trials indicated a reduction in sildenafil clearance when it was co-administered with CYP3A inhibitors. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg TID compared to its exposure at a dose of 20 mg 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).

Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

When a single 100 mg dose of sildenafil was co-administered with erythromycin, a CYP3A inhibitor, at steady state (500 mg BID for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC).

In a study performed in healthy volunteers, co-administration of the HIV protease inhibitor saquinavir, a CYP3A inhibitor, at steady state (1200 mg TID) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC.

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.

Bosentan

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg TID) with bosentan (a moderate inducer of CYP3A, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg BID) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil C_{max} . Co-administration resulted in a 50% increase in AUC of bosentan. The combination of both drugs did not lead to clinically significant changes in blood pressure (supine or standing). Concomitant administration of potent CYP3A inducers is expected to cause greater decreases in plasma levels of sildenafil.

Epoprostenol

The mean reduction of sildenafil (80 mg tid) bioavailability due to co-administration of 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.

CYP Substrates and Beta-blockers

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance or an increase of oral bioavailability when co-administered with CYP3A substrates and the combination of CYP3A substrates and beta-blockers.

In a study of healthy volunteers, sildenafil (100 mg) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors saquinavir and ritonavir, both of which are CYP3A substrates.

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

Oral Contraceptives

Concomitant administration of oral contraceptives (ethinyl estradiol 30 mcg and levonorgestrel 150 mcg) did not affect the pharmacokinetics of sildenafil. Sildenafil had no impact on the plasma levels of oral contraceptives (ethinyl estradiol 30 mcg and levonorgestrel 150 mcg).

Atorvastatin

Concomitant administration of a single 100 mg dose of sildenafil with 10 mg of atorvastatin did not alter the pharmacokinetics of either sildenafil or atorvastatin.

Antacids

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of sildenafil.

Aspirin

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

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 TID. 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/m² 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 TID.

14 CLINICAL STUDIES

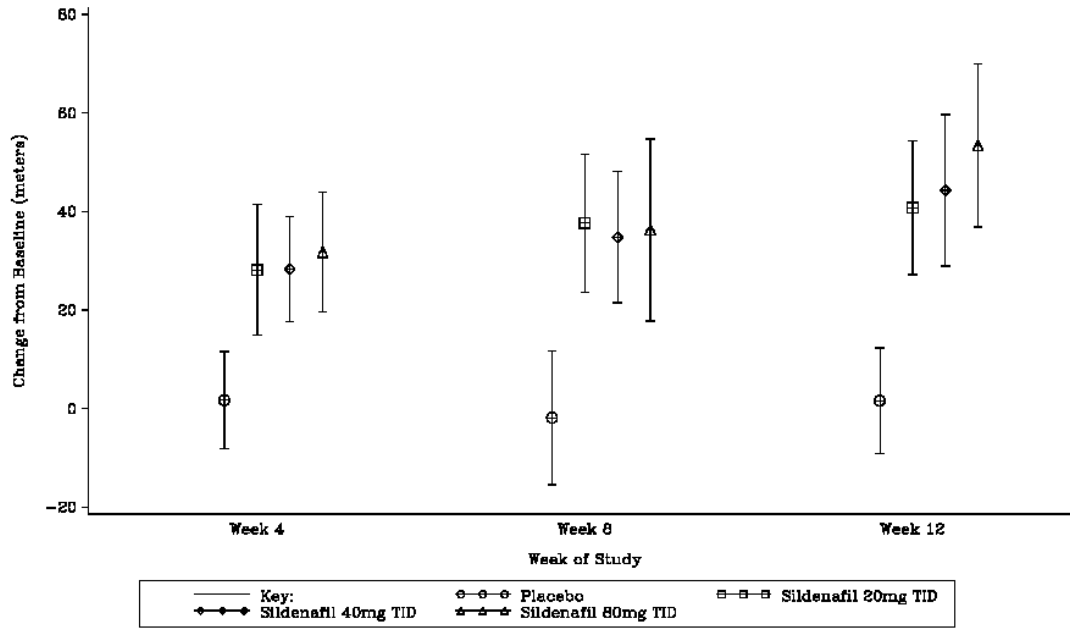
Study 1

A randomized, double-blind, placebo-controlled study was conducted in 277 patients with PAH (defined as a mean pulmonary artery pressure of ≥ 25 mmHg at rest with a pulmonary capillary wedge pressure < 15 mmHg). Patients were predominantly 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. Subjects who had failed to respond to bosentan were also excluded. Patients with left ventricular ejection fraction $< 45\%$ or left ventricular shortening fraction < 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) TID for a period of 12 weeks. They had either 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: 18-81 years) and baseline 6-minute walk distance between 100 and 450 meters (mean 343).

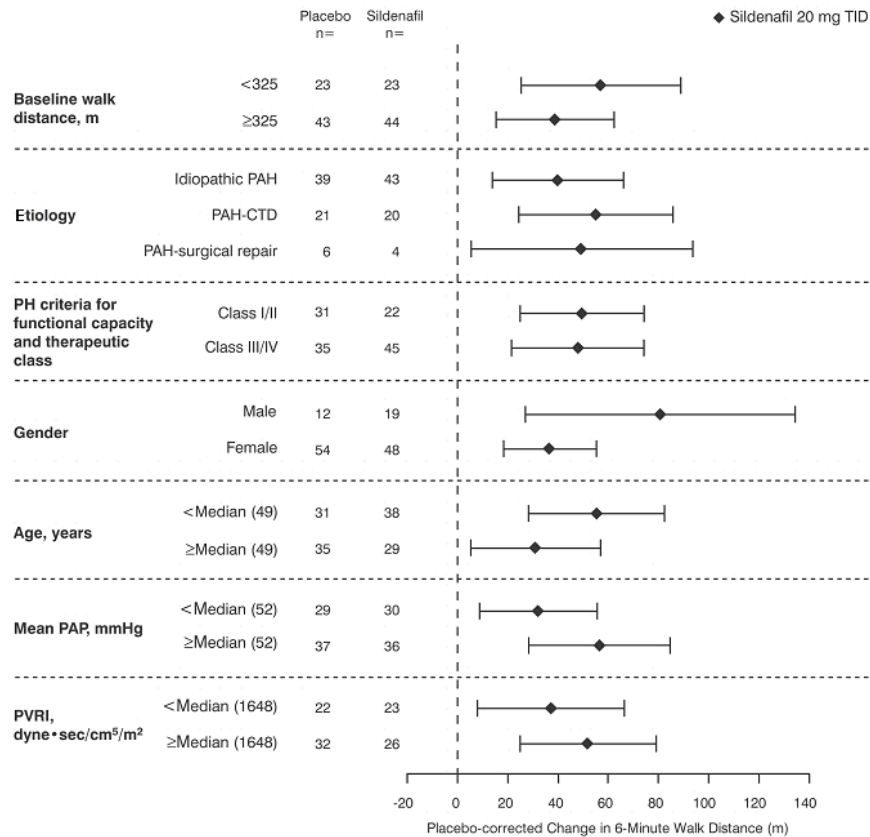
The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance at least 4 hours after the last dose. Placebo-corrected mean increases in walk distance of 45-50 meters were observed with all doses of REVATIO. These increases were significantly different from placebo, but the dose groups were not different from each other (Figure 1), indicating no additional clinical benefit from doses higher than 20 mg TID. The improvement in walk distance was apparent after 4 weeks of treatment and was maintained at week 8 and week 12.

Figure 1. Change from Baseline in 6-Minute Walk Distance (meters): Mean (95% Confidence Interval)



Pre-defined subpopulations in the study were also evaluated for efficacy, including patient differences in baseline walk distance, disease etiology, functional class, gender, age, and secondary hemodynamic parameters (Figure 2).

Figure 2. Placebo Corrected Change From Baseline in 6-Minute Walk Distance (meters) by study subpopulation: 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.

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 can be found in Table 3. The relationship between these effects and improvements in 6-minute walk distance is unknown.

Table 3. Changes from Baseline to Week 12 in Hemodynamic Parameters at REVATIO 20 mg TID Dose

PARAMETER [mean (95% CI)]	Placebo (n = 65)*	REVATIO 20 mg TID (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)

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

Of the 277 treated patients, 259 entered a long-term, uncontrolled extension study. At the end of 1 year, 94% of these patients were still alive. Additionally, walk distance and functional class status appeared to be stable in patients taking sildenafil. Without a control group, these data must be interpreted cautiously.

Study 2

A randomized, double-blind, placebo controlled study was conducted in 267 patients with PAH who were stabilized on intravenous epoprostenol. Patients had to have a mean pulmonary artery pressure (mPAP) \geq 25 mmHg and a pulmonary capillary wedge pressure (PCWP) \leq 15 mmHg at rest via right heart catheterization within 21 days before randomization, and a baseline 6-minute walk test distance \geq 100 m and \leq 450 m (mean 349). 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) when used in combination with intravenous epoprostenol

Patients had primary pulmonary hypertension (80%) or PAH secondary to CTD (20%). Patients had WHO functional class I (1%), II (26%), III (67%), or IV (6%) at baseline. The mean age was 48 years, 80% were female, and 79% were Caucasian.

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

Patients on sildenafil 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).

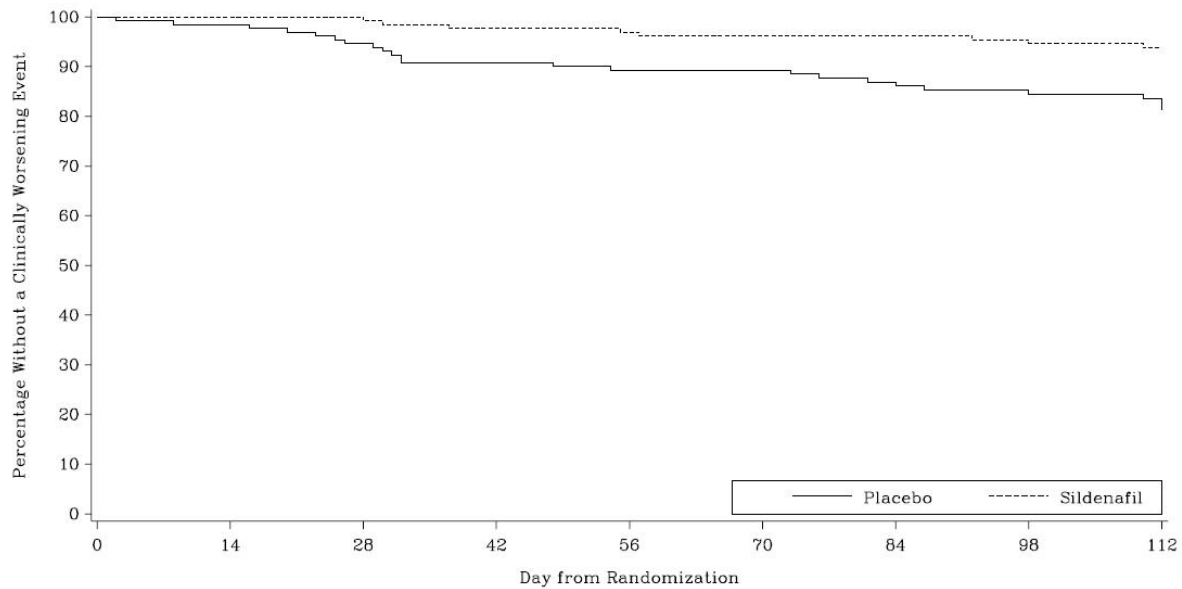
Clinical Worsening

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). Patients with clinical worsening events are summarized in Table 4. Kaplan-Meier estimates and a stratified log-rank test demonstrated that placebo patients were 3 times more likely to experience an event and that patients receiving REVATIO experienced a significant delay in time to clinical worsening versus placebo (p = 0.0074).

Table 4. Clinical Worsening Events

	Placebo (N = 131)		REVATIO (N = 134)	
	First Event	All Events	First Event	All Events
Number of subjects with clinical worsening event n (%)	23 (17.6)		8 (6.0)	
Incidence of Clinical Worsening Events				
Death	3	4	0	0
Lung Transplantation	1	1	0	0
Hospitalization due to PAH	9	11	8	8
Clinical deterioration resulting in:				
Change of Epoprostenol Dose	9	16	0	2
Initiation of Bosentan Therapy	1	1	0	0
Proportion Worsened	0.187		0.062	
95% Confidence Intervals	(0.12 - 0.26)		(0.02 - 0.10)	

Figure 3. Kaplan-Meier Plot of Time to Clinical Worsening (Days), ITT Population



Improvements in functional class were also demonstrated in subjects on sildenafil compared to placebo. More than twice as many sildenafil treated patients (36%) as the placebo group (14%) showed an improvement of at least one functional class.

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

REVATIO Injection is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg sildenafil (12.5mL) presented in a 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 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

1. Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
2. Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.
3. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
4. 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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