

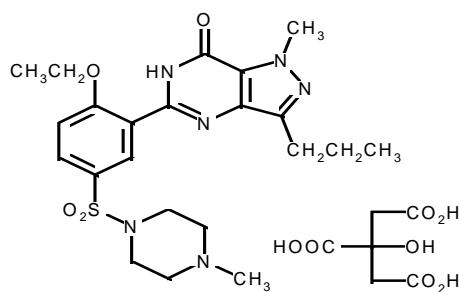
REVATIO[®]

(sildenafil citrate) Tablets

DESCRIPTION

REVATIO[®], an oral 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 male 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 (sildenafil citrate) 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.

CLINICAL PHARMACOLOGY

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, 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, >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 **Pharmacodynamics**).

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*.

Pharmacokinetics and Metabolism

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 CYP3A4 (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. The concomitant use of potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION and PRECAUTIONS/Drug Interactions**).

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).

Pharmacokinetics in Special Populations

Geriatrics: 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 Insufficiency: 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 Insufficiency: In volunteers with 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.

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 pulmonary arterial hypertension patients. The data set 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 statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary hypertension.

In patients with pulmonary hypertension, 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.

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**).

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 t.i.d. to patients with pulmonary arterial hypertension, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg t.i.d. 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 t.i.d. 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 t.i.d. 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.

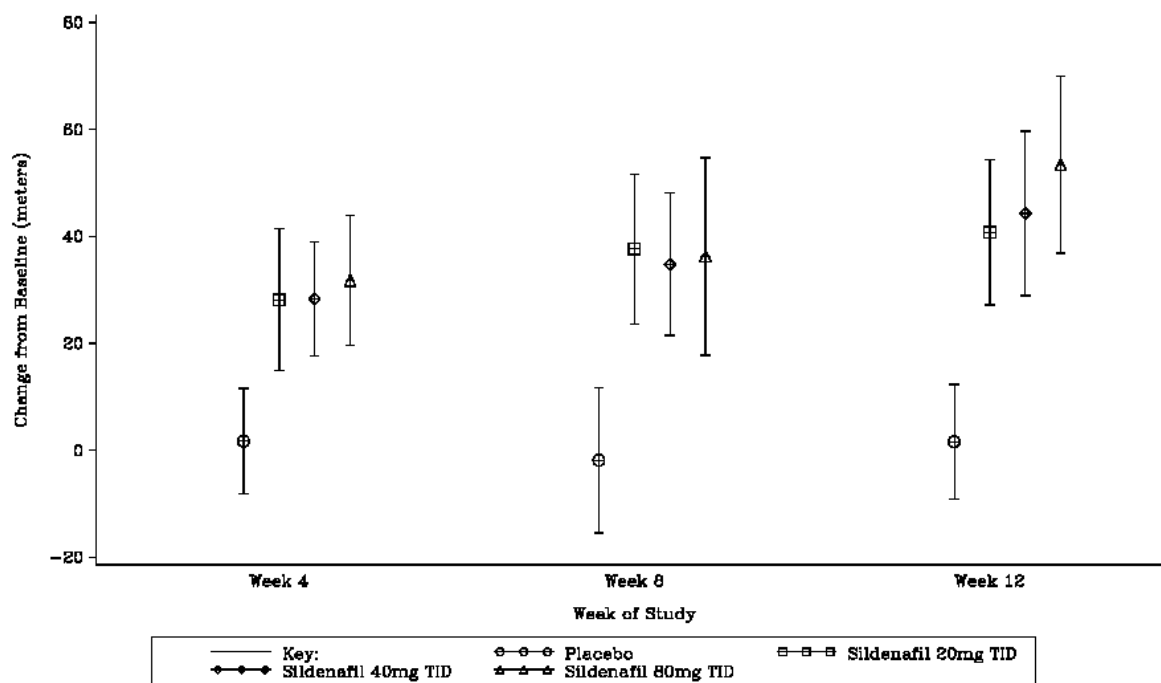
Clinical Studies

A randomized, double-blind, placebo-controlled study was conducted in 277 patients with pulmonary arterial hypertension (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 anticoagulation, digoxin, calcium channel blockers, diuretics or 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) t.i.d. for a period of 12 weeks. They had either primary pulmonary hypertension (63%), PAH associated with connective tissue disease (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 test distance between 100 and 450 meters.

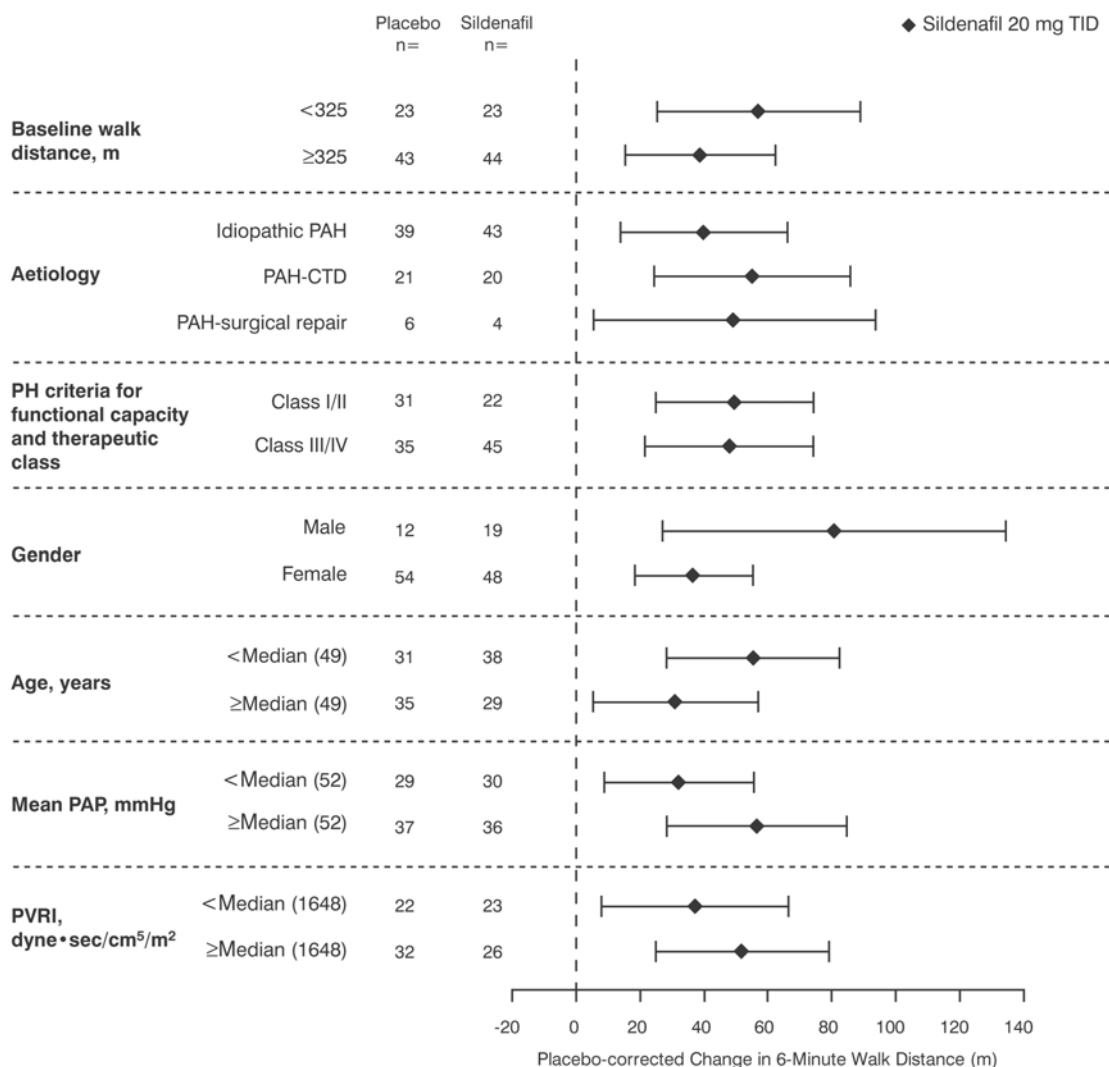
The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance at least 4 hours after the last dose. Placebo-corrected mean increases in walk distance of 45-50 meters were observed with all doses of sildenafil. These increases were highly significantly different from placebo, but the dose groups were not different from each other (Figure 1). 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 pivotal 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. Doses of 20 mg, 40 mg, and 80 mg t.i.d. produced a placebo-corrected decrease in mPAP of -2.7 mmHg, -3.0 mmHg, and -5.1 mmHg, respectively. There was no evidence of a difference in effect between sildenafil 20 mg t.i.d. and the higher doses tested. Data from other hemodynamic parameters can be found in Table 1. The relationship between these effects and improvements in 6-minute walk distance is unknown.

Table 1. Changes from Baseline to Week 12 in Hemodynamic Parameters at Sildenafil 20 mg t.i.d. Dose

PARAMETER [mean (95% CI)]	Placebo (N=65)*	Sildenafil 20 mg t.i.d. (N=65)*
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.

259 of the 277 treated patients 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.

INDICATIONS AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

The efficacy of REVATIO has not been evaluated in patients currently on bosentan therapy.

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY**), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

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

WARNINGS

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of sildenafil, therefore co-administration with REVATIO is not recommended (see **Drug Interactions** and **DOSAGE AND ADMINISTRATION**).

REVATIO has vasodilator properties, resulting in mild and transient decreases in blood pressure (see **PRECAUTIONS**). Prior to prescribing REVATIO, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, for example patients with resting hypotension (BP <90/50), or with 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 sildenafil is administered, the possibility of associated PVOD should be considered.

There is no controlled clinical data on the safety or efficacy of REVATIO in the following groups; if prescribed, this should be done with caution:

- 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 with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
- Patients currently on bosentan therapy.

PRECAUTIONS

General

Before prescribing REVATIO, it is important to note the following:

- Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are co-administered 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 (see **Drug Interactions**), cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported. No cases of syncope or fainting were reported during these interaction studies. Consideration should be given to the fact that 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.
- REVATIO should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (such as 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 erections greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.
- 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 higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). The incidence of epistaxis was also higher in sildenafil-treated patients with 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 and patients with active peptic ulceration.

Information for Patients

Physicians should discuss with patients the contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

Sildenafil is also marketed as VIAGRA[®] for male erectile dysfunction.

Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking all 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 rarely post-marketing in temporal association with the use of all PDE5 inhibitors when used in the treatment of male-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 with patients the increased risk of NAION in individuals 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**).

Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking all 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, Clinical Trials and Post-Marketing Experience**).

Drug Interactions

In PAH patients, the concomitant use of vitamin K antagonists and sildenafil resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo.

Effects of Other Drugs on REVATIO

In vitro studies: Sildenafil metabolism is principally mediated by the CYP3A4 (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.

In vivo studies: Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics.

Population data from patients in clinical trials indicated a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg t.i.d. compared to its exposure at a dose of 20 mg t.i.d. This concentration range covers the same increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A4 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 CYP3A4 inhibitor, at steady state (500 mg twice daily [b.i.d.] 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 CYP3A4 inhibitor, at steady state (1200 mg t.i.d.) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Stronger CYP3A4 inhibitors will have still greater effects on plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**).

In another study in healthy volunteers, co-administration with the HIV protease inhibitor ritonavir, a potent CYP3A4 inhibitor, at steady state (500 mg b.i.d.) 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 (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**). Although the interaction between other protease inhibitors and REVATIO has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.) with the endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil C_{max} . The combination of both drugs did not lead to clinically significant changes in blood pressure (supine or standing). Concomitant administration of potent CYP3A4 inducers is expected to cause greater decreases in plasma levels of sildenafil.

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 (see **PRECAUTIONS: General**).

Concomitant administration of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil.

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.

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

Effects of REVATIO on Other Drugs

***In vitro* studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ($IC_{50} > 150 \mu M$).

In vivo studies: 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.

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

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

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

In healthy subjects, co-administration of 125 mg b.i.d. bosentan and 80 mg t.i.d. sildenafil resulted in a 63% decrease in AUC of sildenafil and a 50% increase in AUC of bosentan.

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 CYP3A4 substrates.

Sildenafil had no impact on the plasma levels of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg).

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 Recommended Human Dose (RHD) of 20 mg t.i.d. 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 t.i.d.

Pregnancy

Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in pregnant rats or rabbits, dosed with 200 mg sildenafil/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the RHD of 20 mg t.i.d. 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 no adequate and well-controlled studies of sildenafil in pregnant women.

Nursing Mothers

It is not known if sildenafil citrate and/or metabolites are excreted in human breast milk. Since many drugs are excreted in human milk, caution should be used when REVATIO is administered to nursing women.

Pediatric Use

Safety and Effectiveness of sildenafil in pediatric pulmonary hypertension patients has not been established.

Geriatric Use

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, but studies did not include sufficient numbers of subjects to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger pulmonary arterial hypertension 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.

ADVERSE REACTIONS

Clinical Trials

Safety data were obtained from the pivotal study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg t.i.d. were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg t.i.d. was low (3%) and the same as placebo (3%).

In the pivotal 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 t.i.d.) and were more frequent in REVATIO patients than placebo patients, are shown in Table 2. Adverse events were generally transient and mild to moderate in nature.

Table 2. Sildenafil Adverse Events in $\geq 3\%$ of Patients and More Frequent than Placebo

ADVERSE EVENT %	Placebo (n=70)	Sildenafil 20 mg t.i.d. (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

At doses higher than the recommended 20 mg t.i.d. 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-tinge to vision, but also increased sensitivity to light or blurred vision.

In the pivotal study, the incidence of retinal hemorrhage at the recommended sildenafil 20 mg t.i.d. 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.

Post-Marketing Experience

In post-marketing experience with sildenafil citrate at doses indicated for male 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 citrate, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

When used to treat male-erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil citrate. 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 **PRECAUTIONS/Information for Patients**).

Cases of sudden decrease or loss of hearing have been reported post-marketing 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 **PRECAUTIONS, Information for Patients**).

Other events:

The following list includes other adverse events that have been identified during post-marketing 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: seizure, seizure recurrence

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.

DOSAGE AND ADMINISTRATION

The recommended dose of REVATIO is 20 mg three times a day (t.i.d.). 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 t.i.d. is not recommended. Dosages lower than 20 mg t.i.d. were not tested. Whether dosages lower than 20 mg t.i.d. are effective is not known.

In general, dose selection for elderly patients 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**)

No dose adjustments are required for renal impaired patients (including severe renal impairment, creatinine clearance <30 mL/min), or for hepatic impaired patients (Child Pugh class A and B).

No dose adjustments are required for the co-administration of REVATIO with erythromycin or saquinavir.

Co-administration of REVATIO with CYP3A4 inducers (including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, rifabutin) may alter plasma levels of either or both medications. Dosage adjustments may be necessary (see **PRECAUTIONS: Drug Interactions**).

Co-administration of potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) with REVATIO substantially increases serum concentrations of sildenafil and is therefore not recommended (see **WARNINGS** and **PRECAUTIONS: Drug Interactions**).

Sildenafil was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors, or nitrates in any form, is therefore contraindicated.

HOW SUPPLIED

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

REVATIO Tablets

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

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

Rx Only



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PATIENT INFORMATION

REVATIO[®] (re-VAH-tee-oh) (sildenafil citrate) tablets

Read the Patient Information that comes with REVATIO before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about REVATIO, ask your doctor or pharmacist.

What is the most important information I should know about REVATIO (sildenafil citrate)?

- **Never take REVATIO with any nitrate medicines. Your blood pressure could drop quickly. It could fall to an unsafe level. Nitrate medicines include:**
 - Medicines that treat chest pain (angina)
 - Nitroglycerin in any form
 - Isosorbide mononitrate or dinitrate
 - Street drugs called “poppers” (amyl nitrate or nitrite)

Ask your doctor or pharmacist if you are not sure if you are taking a nitrate medicine.

What is REVATIO (sildenafil citrate)?

REVATIO is a prescription medicine used to treat **pulmonary arterial hypertension (PAH)**. REVATIO improves the ability to exercise. With PAH, the blood pressure in your lungs is too high. Your heart has to work hard to pump blood into your lungs.

REVATIO has **not** been studied

- in children under 18 years old
- in patients who are also taking a medicine called bosentan (Tracleer[®])

REVATIO contains the same medicine as VIAGRA[®] (sildenafil citrate), which is used to treat erectile dysfunction (impotence).

Who should not take REVATIO (sildenafil citrate)?

Do not take REVATIO if you

- take nitrate medicines. See “**What is the most important information I should know about REVATIO?**”
- are allergic to sildenafil citrate or any other ingredient in REVATIO. See “What are the ingredients in REVATIO?” at the end of this leaflet.

What should I tell my doctor before taking REVATIO (sildenafil citrate)?

Tell your doctor about all of your medical conditions, including if you

- have had a heart attack, stroke, or irregular heartbeats in the last 6 months
- have chest pain (angina)
- have a disease called pulmonary veno-occlusive disease (PVOD)

- have high or low blood pressure or blood circulation problems
- have an eye problem called retinitis pigmentosa
- have or had loss of sight in one or both eyes
- have liver or kidney problems
- have any problem with the shape of your penis
- lose a large amount of body fluids (dehydration). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot or don't drink enough liquids.
- have any blood cell problems such as cancer of blood cells or bone marrow or sickle cell anemia
- have a stomach ulcer or any bleeding problems
- are pregnant or planning to become pregnant. It is not known if REVATIO could harm your unborn baby.
- are breastfeeding. It is not known if REVATIO passes into your breast milk or if it could harm your baby.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. REVATIO and certain other medicines can cause side effects if you take them together. The doses of some of your medicines may need to be adjusted while you take REVATIO.

Especially tell your doctor if you

- Take nitrate medicines. See **“What is the most important information I should know about REVATIO?”**
- Take ritonavir (Norvir[®]) or other medicines used to treat HIV infection
- Use ketoconazole (Nizoral[®])

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take REVATIO (sildenafil citrate)?

- Take REVATIO exactly as your doctor tells you.
- REVATIO is a tablet you take by mouth. Take a REVATIO tablet 3 times a day about 4 to 6 hours apart.
- Take REVATIO at the same times every day, with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, skip the missed dose, and take your next dose at the regular time.
- Do not take more than one dose of REVATIO at a time.
- Do not change your dose or stop taking REVATIO on your own. Talk to your doctor first.
- **If you take too much REVATIO, call your doctor or poison control center, or go to an emergency room.**

What are the possible side effects of REVATIO (sildenafil citrate)?

The following side effects were reported in patients taking REVATIO. Some of these were serious.

- **low blood pressure.** Low blood pressure may cause you to feel faint or dizzy. Lie down if you feel faint or dizzy.

- **more shortness of breath than usual.** Tell your doctor if you get more short of breath after you start REVATIO. More shortness of breath than usual may be due to your underlying medical condition.

The following side effects were reported rarely in patients taking sildenafil:

- **decreased eyesight or loss of sight in one or both eyes (NAION).** If you notice a sudden decrease or loss of eyesight, talk to your doctor right away. It is not possible to determine if these events are related to oral medicines for the treatment of erectile dysfunction, including sildenafil, or to other medical problems, or combination of these factors.
- **sudden decrease or loss of hearing.** If you notice a sudden decrease or loss of hearing, talk to your doctor right away. It is not possible to determine whether these events are related directly to this class of oral medicines, including sildenafil, or to other diseases or medications, to other factors, or to a combination of factors.
- **heart attack, stroke, irregular heartbeats, and death.** Most of these happened in men who already had heart problems.
- **erections that last several hours.** Tell your doctor right away if you have an erection that lasts more than 4 hours.

The most common side effects are nosebleed, headache, upset stomach, getting red or hot in the face (flushing), and trouble sleeping.

Tell your doctor if you have any side effect that bothers you or doesn't go away.

These are not all the possible side effects of REVATIO. For more information, ask your doctor or pharmacist.

How should I store REVATIO (sildenafil citrate)?

- Store REVATIO at room temperature, 59-86°F (15-30°C).
- **Keep REVATIO and all medicines away from children.**

General information about REVATIO (sildenafil citrate)

Medicines are sometimes prescribed for conditions that are not in the patient 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 you have. It could harm them.

This patient leaflet summarizes the most important information about REVATIO. If you would like more information about REVATIO:

- Ask your doctor or pharmacist for information about REVATIO that is written for health professionals.
- Go to www.REVATIO.com or call 1-800-879-3477.

What are the ingredients in REVATIO (sildenafil citrate)?

Active ingredients: sildenafil citrate

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

Rx only



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