APPLICATION NUMBER:
21-845

APPROVED LABELING
REVATIO™
(sildenafil citrate) Tablets, 20 mg
Rx Only

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 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:

\[
\text{CH}_3\text{CH}_2\text{O} \quad \text{HN} \quad \text{N} \quad \text{N} \quad \text{CH}_3 \quad \text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{O}_2\text{S} \quad \text{N} \quad \text{N} \quad \text{CH}_2 \quad \text{HOOC} - \text{CO}_2\text{H} \quad \text{OH} \quad \text{CO}_2\text{H}
\]

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 antiaggregatory 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 absolute bioavailability of about 40%. 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 $T_{\text{max}}$ of 60 minutes and a mean reduction in $C_{\text{max}}$ of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

**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, cinemidine, 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, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

**Renal Insufficiency:** In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CLcr < 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and $C_{\text{max}}$ compared to age-matched volunteers with no renal impairment.
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 8.4/5.5 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
CONTRAINICATIONS).

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 patients, 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
analognues, 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)

<table>
<thead>
<tr>
<th>Placebo n=</th>
<th>Sildenafil n=</th>
<th>Sildenafil 20 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline walk distance, m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;325</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>≥325</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Idiopathic PAH</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNH-CTD</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>PAH-surgical repair</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PH criteria for functional capacity and therapeutic class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I/II</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Class III/IV</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median (49)</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>≥Median (49)</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Mean PAP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median (52)</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>≥Median (52)</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>PVRI, dyne·sec/cm²/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median (1648)</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>≥Median (1648)</td>
<td>32</td>
<td>26</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>Placebo (N=65)*</th>
<th>Sildenafil 20 mg t.i.d. (N=65)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR (dyn·s/cm²)</td>
<td>49 (-54, 153)</td>
<td>-122 (-217, -27)</td>
</tr>
<tr>
<td>SVR (dyn·s/cm²)</td>
<td>-78 (-197, 41)</td>
<td>-167 (-307, -26)</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>0.3 (-0.9, 1.5)</td>
<td>-0.8 (-1.9, 0.3)</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>-0.1 (-0.4, 0.2)</td>
<td>0.4 (0.1, 0.7)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>-1.3 (-4.1, 1.4)</td>
<td>-3.7 (-5.9, -1.4)</td>
</tr>
</tbody>
</table>

*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 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.
279 Information for Patients
280 Physicians should discuss with patients the contraindication of REVATIO with regular and/or
281 intermittent use of organic nitrates.
282
283 Drug Interactions
284 In PAH patients, the concomitant use of vitamin K antagonists and sildenafil resulted in a greater
285 incidence of reports of bleeding (primarily epistaxis) versus placebo.
286
287 Effects of Other Drugs on REVATIO
288 In vitro studies: Sildenafil metabolism is principally mediated by the CYP3A4 (major route) and
289 CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes
290 may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil
291 clearance.
292
293 In vivo studies: Population pharmacokinetic analysis of clinical trial data indicated a reduction
294 in sildenafil clearance and/or an increase of oral bioavailability when co-administered with
295 CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were
296 the only factors with a statistically significant impact on sildenafil pharmacokinetics.
297
298 Population data from patients in clinical trials indicated a reduction in sildenafil clearance when
299 it was co-administered with CYP3A4 inhibitors. Sildenafil exposure without concomitant
300 medication is shown to be 5-fold higher at a dose of 80 mg t.i.d. compared to its exposure at a
301 dose of 20 mg t.i.d. This concentration range covers the same increased sildenafil exposure
302 observed in specifically-designed drug interaction studies with CYP3A4 inhibitors (except for
303 potent inhibitors such as ketoconazole, itraconazole, and ritonavir). Cimetidine (800 mg), a
304 nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-
305 administered with sildenafil (50 mg) to healthy volunteers. When a single 100 mg dose of
306 sildenafil was co-administered with erythromycin, a CYP3A4 inhibitor, at steady state (500 mg
307 twice daily [b.i.d.] for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC).
308 In a study performed in healthy volunteers, co-administration of the HIV protease inhibitor
309 saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg t.i.d.) with sildenafil (100 mg single
310 dose) resulted in a 140% increase in sildenafil C_max and a 210% increase in sildenafil AUC.
311 Stronger CYP3A4 inhibitors will have still greater effects on plasma levels of sildenafil (see
312 DOSAGE AND ADMINISTRATION).
313
314 In another study in healthy volunteers, co-administration with the HIV protease inhibitor
315 ritonavir, a potent CYP3A4 inhibitor, at steady state (500 mg b.i.d.) with sildenafil (100 mg
316 single dose) resulted in a 300% (4-fold) increase in sildenafil C_max and a 1000% (11-fold)
317 increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still
318 approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed
319 alone. This is consistent with ritonavir’s marked effects on a broad range of P450 substrates (see
320 WARNINGS and DOSAGE AND ADMINISTRATION). Although the interaction between
321 other protease inhibitors and REVATIO has not been studied, their concomitant use is expected
322 to increase sildenafil levels.
323
324 In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.)
325 with the endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and
326 possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of
327 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 (IC50 >150 μM).

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%.

Sildenafil at steady state (80 mg t.i.d.) resulted in a 50% increase in AUC and a 42% increase in
C_max of bosentan (125 mg b.i.d.).

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 lymphocyte 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 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 up to 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
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>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>Placebo (n=70)</th>
<th>Sildenafil 20 mg t.i.d. (n=69)</th>
<th>Placebo Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea exacerbated</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Rhinitis nos</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea nos</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastritis nos</td>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
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</tr>
</tbody>
</table>

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 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 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.
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 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:

<table>
<thead>
<tr>
<th>Package Configuration</th>
<th>Tablet Strength (mg)</th>
<th>NDC</th>
<th>Engraving on Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottle of 90</td>
<td>20 mg</td>
<td>0069-4190-68</td>
<td>RVT20</td>
</tr>
</tbody>
</table>

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Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
6/3/05 09:15:20 PM