

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-845

APPROVED LABELING

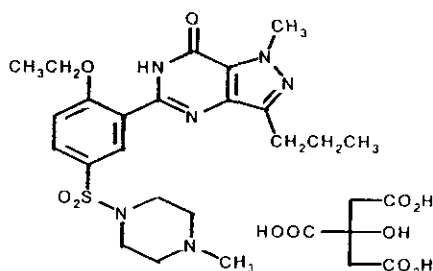
REVATIO™

(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-1*H*-pyrazolo [4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



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

42 an enzyme found in the retina and involved in the phototransduction pathway of the retina. This
43 lower selectivity is thought to be the basis for abnormalities related to color vision observed with
44 higher doses or plasma levels (see **Pharmacodynamics**).

45
46 In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also
47 found in other tissues including vascular and visceral smooth muscle and in platelets. The
48 inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-
49 aggregatory activity of nitric oxide observed *in vitro*, and the mild peripheral arterial-venous
50 dilatation *in vivo*.

51

52 **Pharmacokinetics and Metabolism**

53 **Absorption and Distribution:** REVATIO is rapidly absorbed after oral administration, with
54 absolute bioavailability of about 40%. Maximum observed plasma concentrations are reached
55 within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When
56 REVATIO is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in
57 T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of
58 distribution (V_{ss}) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and
59 its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma
60 proteins. Protein binding is independent of total drug concentrations.

61

62 **Metabolism and Excretion:** Sildenafil is cleared predominantly by the CYP3A4 (major route)
63 and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major
64 circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further
65 metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and
66 an *in vitro* potency for PDE5 approximately 50% of the parent drug. In healthy volunteers,
67 plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so
68 that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients
69 with pulmonary arterial hypertension, however, the ratio of the metabolite to sildenafil is higher.
70 Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. The
71 concomitant use of potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir
72 ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated
73 with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION** and
74 **PRECAUTIONS/Drug Interactions**).

75

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

79

80 **Pharmacokinetics in Special Populations**

81 **Geriatrics:** Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil,
82 with free plasma concentrations approximately 40% greater than those seen in healthy younger
83 volunteers (18-45 years).

84

85 **Renal Insufficiency:** In volunteers with mild (CL_{cr} = 50-80 mL/min) and moderate (CL_{cr} = 30-
86 49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg)
87 was not altered. In volunteers with severe (CL_{cr} < 30 mL/min) renal impairment, sildenafil
88 clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-
89 matched volunteers with no renal impairment.

90

91 **Hepatic Insufficiency:** In volunteers with hepatic cirrhosis (Child-Pugh class A and B),
92 sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared
93 to age-matched volunteers with no hepatic impairment. Patients with severe hepatic impairment
94 (Child-Pugh class C) have not been studied.
95

96 **Population pharmacokinetics**

97 Age, gender, race, and renal and hepatic function were included as factors assessed in the
98 population pharmacokinetic model to evaluate sildenafil pharmacokinetics in pulmonary arterial
99 hypertension patients. The data set available for the population pharmacokinetic evaluation
100 contained a wide range of demographic data and laboratory parameters associated with hepatic
101 and renal function. None of these factors had a statistically significant impact on sildenafil
102 pharmacokinetics in patients with pulmonary hypertension.
103

104 In patients with pulmonary hypertension, the average steady-state concentrations were 20-50%
105 higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels
106 compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral
107 bioavailability of sildenafil in patients with pulmonary hypertension compared to healthy
108 volunteers.
109

110 **Pharmacodynamics**

111 **Effects of REVATIO on Blood Pressure:** Single oral doses of sildenafil (100 mg) administered
112 to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in
113 systolic/diastolic blood pressure of 8.4/5.5 mmHg). The decrease in blood pressure was most
114 notable approximately 1-2 hours after dosing, and was not different from placebo at 8 hours.
115 Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg doses of sildenafil,
116 therefore the effects are not related to dose or plasma levels within this dosage range. Larger
117 effects were recorded among patients receiving concomitant nitrates (see
118 **CONTRAINDICATIONS**).
119

120 Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant
121 effects on ECG. After chronic dosing of 80 mg t.i.d. to patients with pulmonary arterial
122 hypertension, no clinically relevant effects on ECG were reported.
123

124 After chronic dosing of 80 mg t.i.d. sildenafil to healthy patients, the largest mean change from
125 baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 mmHg and
126 8.4 mmHg, respectively.
127

128 After chronic dosing of 80 mg t.i.d. sildenafil to patients with systemic hypertension, the mean
129 change from baseline in systolic and diastolic blood pressures was a decrease of 9.4 mmHg and
130 9.1 mmHg, respectively.
131

132 After chronic dosing of 80 mg t.i.d. sildenafil to patients with pulmonary arterial hypertension,
133 lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease
134 in both of 2 mmHg).
135

136 **Effects of REVATIO on Vision:** At single oral doses of 100 mg and 200 mg, transient dose-
137 related impairment of color discrimination (blue/green) was detected using the Farnsworth-
138 Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is
139 consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An

140 evaluation of visual function at doses up to 200 mg revealed no effects of REVATIO on visual
 141 acuity, intraocular pressure, or pupillometry.

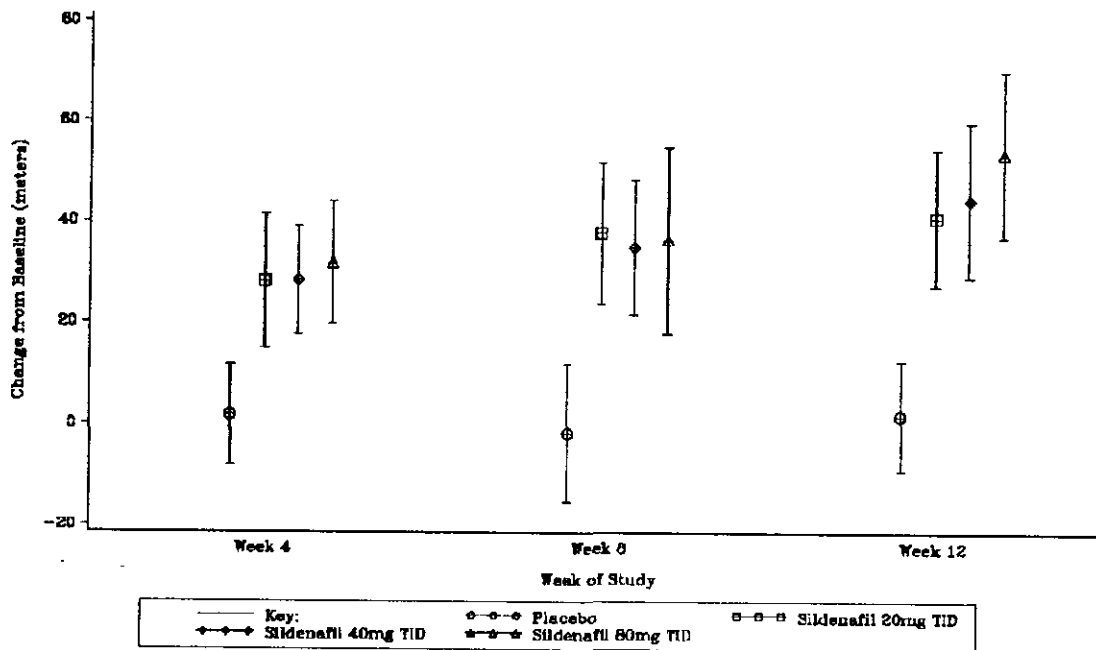
142
 143 **Clinical Studies**

144 A randomized, double-blind, placebo-controlled study was conducted in 277 patients with
 145 pulmonary arterial hypertension (PAH, defined as a mean pulmonary artery pressure of ≥ 25
 146 mmHg at rest with a pulmonary capillary wedge pressure < 15 mmHg). Patients were
 147 predominantly functional classes II-III. Allowed background therapy included a combination of
 148 anticoagulation, digoxin, calcium channel blockers, diuretics or oxygen. The use of prostacyclin
 149 analogues, endothelin receptor antagonists, and arginine supplementation were not permitted.
 150 Subjects who had failed to respond to bosentan were also excluded. Patients with left ventricular
 151 ejection fraction $< 45\%$ or left ventricular shortening fraction < 0.2 also were not studied.

152
 153 Patients were randomized to receive placebo (n=70) or REVATIO 20 mg (n=69), 40 mg (n=67)
 154 or 80 mg (n=71) t.i.d. for a period of 12 weeks. They had either primary pulmonary
 155 hypertension (63%), PAH associated with connective tissue disease (30%), or PAH following
 156 surgical repair of left-to-right congenital heart lesions (7%). The study population consisted of
 157 25% men and 75% women with a mean age of 49 years (range: 18-81 years) and baseline 6-
 158 minute walk test distance between 100 and 450 meters.

159
 160 The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk
 161 distance at least 4 hours after the last dose. Placebo-corrected mean increases in walk distance of
 162 45-50 meters were observed with all doses of sildenafil. These increases were highly
 163 significantly different from placebo, but the dose groups were not different from each other
 164 (Figure 1). The improvement in walk distance was apparent after 4 weeks of treatment and was
 165 maintained at week 8 and week 12.

166
 167 **Figure 1: Change from Baseline in 6-Minute Walk Distance (meters): Mean (95%
 168 Confidence Interval)**

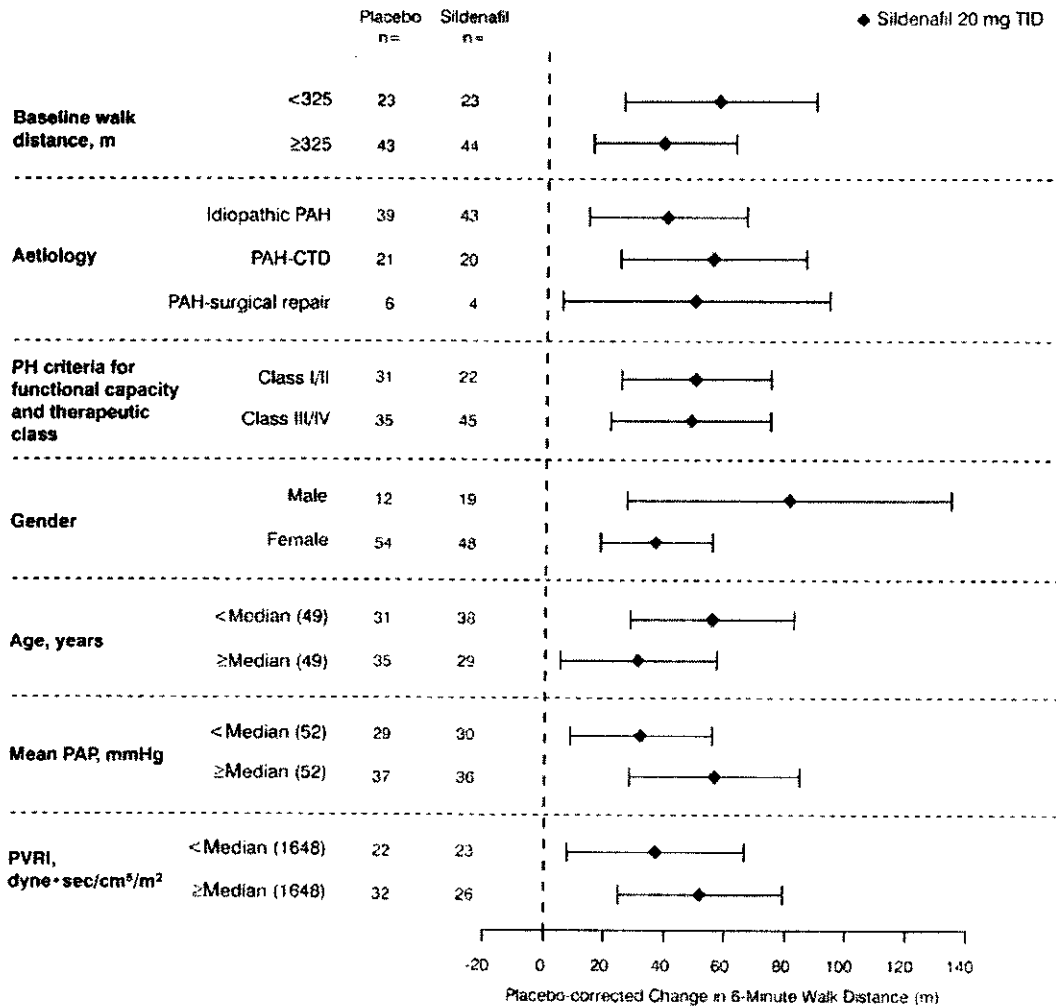


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171 Pre-defined subpopulations in the pivotal study were also evaluated for efficacy, including
 172 patient differences in baseline walk distance, disease etiology, functional class, gender, age, and
 173 secondary hemodynamic parameters (Figure 2).
 174

175 **Figure 2: Placebo Corrected Change From Baseline in 6-Minute Walk Distance (meters) by**
 176 **study subpopulation: Mean (95% Confidence Interval)**



177
 178 **Key:** PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PH, pulmonary hypertension;
 179 PAP = pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; TID = three times daily.
 180

181 Patients on all REVATIO doses achieved a statistically significant reduction in mean pulmonary
 182 arterial pressure (mPAP) compared to those on placebo. Doses of 20 mg, 40 mg, and 80 mg t.i.d.
 183 produced a placebo-corrected decrease in mPAP of -2.7 mmHg, -3.0 mmHg, and -5.1 mmHg,
 184 respectively. There was no evidence of a difference in effect between sildenafil 20 mg t.i.d. and
 185 the higher doses tested. Data from other hemodynamic parameters can be found in Table 1. The
 186 relationship between these effects and improvements in 6-minute walk distance is unknown.
 187

188 **Table 1. Changes from Baseline to Week 12 in Hemodynamic Parameters at Sildenafil**
 189 **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)

190 *The number of patients per treatment group varied slightly for each parameter due to missing assessments.
 191

192 259 of the 277 treated patients entered a long-term, uncontrolled extension study. At the end of
 193 1 year, 94% of these patients were still alive. Additionally, walk distance and functional class
 194 status appeared to be stable in patients taking sildenafil. Without a control group, these data
 195 must be interpreted cautiously.
 196

197 INDICATIONS AND USAGE

198 REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to
 199 improve exercise ability.
 200

201 The efficacy of REVATIO has not been evaluated in patients currently on bosentan therapy.
 202
 203

204 CONTRAINDICATIONS

205 Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL**
 206 **PHARMACOLOGY**), sildenafil was shown to potentiate the hypotensive effects of nitrates,
 207 and its administration to patients who are using organic nitrates, either regularly and/or
 208 intermittently, in any form is therefore contraindicated.
 209

210 REVATIO is contraindicated in patients with a known hypersensitivity to any component of the
 211 tablet.
 212

213 WARNINGS

214 The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4
 215 inhibitor) substantially increases serum concentrations of sildenafil, therefore co-administration
 216 with REVATIO is not recommended (see **Drug Interactions** and **DOSAGE AND**
 217 **ADMINISTRATION**).
 218

219 REVATIO has vasodilator properties, resulting in mild and transient decreases in blood pressure
 220 (see **PRECAUTIONS**). Prior to prescribing REVATIO, physicians should carefully consider
 221 whether their patients with certain underlying conditions could be adversely affected by such
 222 vasodilatory effects, for example patients with resting hypotension (BP <90/50), or with fluid
 223 depletion, severe left ventricular outflow obstruction, or autonomic dysfunction.
 224

225 Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with
 226 pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of
 227 REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients
 228
 229

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230 is not recommended. Should signs of pulmonary edema occur when sildenafil is administered,
231 the possibility of associated PVOD should be considered.
232

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

- 235 ▪ Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia
236 within the last 6 months;
- 237 ▪ Patients with coronary artery disease causing unstable angina;
- 238 ▪ Patients with hypertension (BP >170/110);
- 239 ▪ Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of
240 retinal phosphodiesterases).
- 241 ▪ Patients currently on bosentan therapy.

242
243

PRECAUTIONS

245 General

246 Before prescribing REVATIO, it is important to note the following:
247

- 248 ▪ Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are co-administered
249 with alpha-blockers. PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking
250 agents are both vasodilators with blood pressure lowering effects. When vasodilators are
251 used in combination, an additive effect on blood pressure may be anticipated. In some
252 patients, concomitant use of these two drug classes can lower blood pressure significantly,
253 leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers
254 (see **Drug Interactions**), cases of symptomatic hypotension consisting of dizziness and
255 lightheadedness were reported. No cases of syncope or fainting were reported during these
256 interaction studies. Consideration should be given to the fact that safety of combined use of
257 PDE5 inhibitors and alpha-blockers may be affected by other variables, including
258 intravascular volume depletion and concomitant use of anti-hypertensive drugs.
259
- 260 ▪ REVATIO should be used with caution in patients with anatomical deformation of the penis
261 (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have
262 conditions, which may predispose them to priapism (such as sickle cell anemia, multiple
263 myeloma or leukemia).
264
- 265 ▪ In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. *In*
266 *vitro* studies with human platelets indicate that sildenafil potentiates the anti-aggregatory
267 effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and
268 sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this
269 interaction has not been studied in humans.
270
- 271 ▪ The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil
272 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). The incidence of
273 epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K
274 antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).
275
- 276 ▪ The safety of REVATIO is unknown in patients with bleeding disorders and patients with
277 active peptic ulceration.
278

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

328 lead to clinically significant changes in blood pressure (supine or standing). Concomitant
329 administration of potent CYP3A4 inducers is expected to cause greater decreases in plasma
330 levels of sildenafil.

331

332 In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker
333 doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic
334 hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional
335 reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and
336 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure
337 of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were
338 infrequent reports of patients who experienced symptomatic postural hypotension. These reports
339 included dizziness and light-headedness, but not syncope (see **PRECAUTIONS: General**).

340

341 Concomitant administration of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel
342 150 µg) did not affect the pharmacokinetics of sildenafil.

343

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

346

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

349

350 **Effects of REVATIO on Other Drugs**

351 *In vitro* studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9,
352 2C19, 2D6, 2E1 and 3A4 (IC₅₀ >150 µM).

353

354 *In vivo* studies: When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or
355 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was
356 8 mmHg systolic and 7 mmHg diastolic.

357

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

360

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

362

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

365

366 Sildenafil at steady state (80 mg t.i.d.) resulted in a 50% increase in AUC and a 42% increase in
367 C_{max} of bosentan (125 mg b.i.d.).

368

369 In a study of healthy volunteers, sildenafil (100 mg) did not affect the steady-state
370 pharmacokinetics of the HIV protease inhibitors saquinavir and ritonavir, both of which are
371 CYP3A4 substrates.

372

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

375

376 Carcinogenesis, Mutagenesis, Impairment of Fertility

377 Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a
378 dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite
379 33 and 37 times, for male and female rats, respectively, the human exposure at the
380 Recommended Human Dose (RHD) of 20 mg t.i.d.. Sildenafil was not carcinogenic when
381 administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a
382 maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m² basis.

383

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

387

388 There was no impairment of fertility in male or female rats given up to 60 mg sildenafil /kg/day,
389 a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite
390 19 and 38 times, for males and females, respectively, the human exposure at the RHD of 20 mg
391 t.i.d.

392

393 Pregnancy

394 **Pregnancy Category B.** No evidence of teratogenicity, embryotoxicity or fetotoxicity was
395 observed in pregnant rats or rabbits, dosed with up to 200 mg sildenafil /kg/day during
396 organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the RHD of 20
397 mg t.i.d.. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was
398 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis). There are no adequate and
399 well-controlled studies of sildenafil in pregnant women.

400

401 Nursing Mothers

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

405

406 Pediatric Use

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

409

410 Geriatric Use

411 Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, but studies
412 did not include sufficient numbers of subjects to determine whether they respond differently
413 from younger subjects. Other reported clinical experience has not identified differences in
414 response between the elderly and younger pulmonary arterial hypertension patients. In general,
415 dose selection for an elderly patient should be cautious, reflecting the greater frequency of
416 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

417

418

419

ADVERSE REACTIONS

420 Safety data were obtained from the pivotal study and an open-label extension study in
421 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg t.i.d. were studied.

422

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

425
 426 In the pivotal placebo-controlled trial in pulmonary arterial hypertension, the adverse drug
 427 reactions that were reported by at least 3% of REVATIO patients treated at the recommended
 428 dosage (20 mg t.i.d.) and were more frequent in REVATIO patients than placebo patients, are
 429 shown in Table 2. Adverse events were generally transient and mild to moderate in nature.

430
 431 **Table 2. Sildenafil Adverse Events in ≥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

432
 433 At doses higher than the recommended 20 mg t.i.d. there was a greater incidence of some
 434 adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual
 435 disturbances were identified as mild and transient, and were predominately color-tinge to vision,
 436 but also increased sensitivity to light or blurred vision.

437
 438 In the pivotal study, the incidence of retinal hemorrhage at the recommended sildenafil
 439 20 mg t.i.d. dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9%
 440 versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all
 441 doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these
 442 events had risk factors for hemorrhage including concurrent anticoagulant therapy.

443
 444 In post-marketing experience with sildenafil citrate at doses indicated for male erectile
 445 dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial
 446 infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient
 447 ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral
 448 hemorrhages have been reported in temporal association with the use of the drug. Most, but not
 449 all, of these patients had preexisting cardiovascular risk factors. Many of these events were
 450 reported to occur during or shortly after sexual activity, and a few were reported to occur shortly
 451 after the use of sildenafil without sexual activity. Others were reported to have occurred hours to
 452 days after use concurrent with sexual activity. It is not possible to determine whether these
 453 events are related directly to sildenafil citrate, to sexual activity, to the patient's underlying
 454 cardiovascular disease, or to a combination of these or other factors.

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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

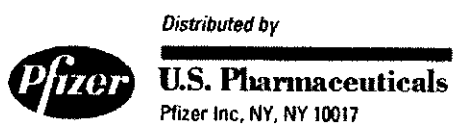
REVATIO (sildenafil citrate) is supplied as white, film-coated, round tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

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

500

NDA 21-845

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



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/s/

Norman Stockbridge
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