

SILDENAFIL- sildenafil citrate tablet, film coated
Northstar RxLLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use sildenafil tablets safely and effectively. See full prescribing information for sildenafil tablets.

Sildenafil tablets, for oral use

Initial U.S. Approval: 1998

----- **RECENT MAJOR CHANGES** -----

Warnings and Precautions (5)

08/2012

----- **INDICATIONS AND USAGE** -----

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability. A study establishing effectiveness was short-term (12 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were primarily idiopathic or associated with connective tissue disease. (1)

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

----- **DOSAGE AND ADMINISTRATION** -----

Tablet: 20 mg three times a day, 4-6 hours apart (2.1)

----- **DOSAGE FORMS AND STRENGTHS** -----

- *Tablets:* 20 mg (3)

----- **CONTRAINDICATIONS** -----

- Use with organic nitrates (4)
- History of hypersensitivity reaction to sildenafil or any component of the tablet (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Increased mortality with increasing doses in pediatric patients. Not recommended for use in pediatric patients. (5.1)
- Vasodilation effects may be more common in patients with hypotension or on antihypertensive therapy. (5.2)
- Use in pulmonary veno-occlusive disease may cause pulmonary edema and is not recommended. (5.3)
- Hearing or visual impairment: Seek medical attention if sudden decrease or loss of vision or hearing occurs. (5.5, 5.6)
- Pulmonary hypertension secondary to sickle cell disease: Sildenafil tablets may cause serious vaso-occlusive crises. (5.9)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions greater than or equal to 3% and more frequent than placebo were epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Northstar Rx LLC at 1-800-206-7821 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- Concomitant alpha-blockers or amlodipine: Note additive blood pressure lowering effects. (7)
- Use with ritonavir and other potent CYP3A inhibitors: Not recommended. (7, 12.3)
- Concomitant PDE-5 inhibitors: Avoid use with Viagra or other PDE-5 inhibitors. (5.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

A study establishing effectiveness was short-term (12 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and primarily idiopathic etiology or associated with connective tissue disease (CTD).

Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Sildenafil Tablets

The recommended dose of sildenafil tablets is 20 mg three times a day (TID). Administer sildenafil doses 4-6 hours apart.

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

3 DOSAGE FORMS AND STRENGTHS

Sildenafil Tablets

Sildenafil tablets are supplied as white, round shaped convex film-coated tablets debossed with “WPI” on one side and “3780” on the other side containing sildenafil citrate, USP equivalent to 20 mg of sildenafil.

4 CONTRAINDICATIONS

Sildenafil is contraindicated in patients with:

- Concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension [*see Warnings and Precautions (5.2)*].
- Known hypersensitivity to sildenafil or any component of the tablet. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

5 WARNINGS AND PRECAUTIONS

5.1 Mortality with Pediatric Use

In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing sildenafil dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of sildenafil, particularly chronic use, is not recommended in children. [*see Use in Specific Populations (8.4)*].

5.2 Hypotension

Sildenafil has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing sildenafil, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with sildenafil.

5.3 Worsening Pulmonary Vascular Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary venoocclusive disease (PVOD). Since there are no clinical data on administration of sildenafil to patients with venoocclusive disease, administration of sildenafil to such patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, consider the possibility of associated PVOD.

5.4 Epistaxis

The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to CTD. This effect was not seen in idiopathic PAH (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of sildenafil is unknown in patients with bleeding disorders or active peptic ulceration.

5.5 Visual Loss

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including sildenafil. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

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

5.6 Hearing Loss

Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including sildenafil. In some of the cases, medical conditions and other factors were reported that may have played a role. 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 sildenafil, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including sildenafil.

5.7 Combination with other PDE-5 inhibitors

Sildenafil is also marketed as VIAGRA[®]. The safety and efficacy of combinations of sildenafil tablets with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking sildenafil tablets not to take VIAGRA or other PDE-5 inhibitors.

5.8 Priapism

Use sildenafil tablets with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

5.9 Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia

In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received sildenafil than by those randomized to placebo. The effectiveness and safety of sildenafil in the treatment of PAH secondary to sickle cell anemia has not been established.

6 ADVERSE REACTIONS

The following serious adverse events are discussed elsewhere in the labeling:

- Mortality with pediatric use [see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]
- Hypotension [see Warnings and Precautions (5.2)]
- Vision loss [see Warnings and Precautions (5.5)]
- Hearing loss [see Warnings and Precautions (5.6)]
- Priapism [see Warnings and Precautions (5.8)]
- Vaso-occlusive crisis [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data of sildenafil in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 sildenafil-treated patients with PAH, WHO Group I Diagnostic Classification [see Clinical Studies (14)].

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

In Study 1, the adverse reactions that were reported by at least 3% of sildenafil-treated patients (20 mg TID) and were more frequent in sildenafil-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1. Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in Sildenafil-Treated Patients than Placebo-Treated Patients and Incidence >3% in Sildenafil-Treated Patients)

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

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse reactions 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.

The incidence of retinal hemorrhage with sildenafil 20 mg TID 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 20 mg TID and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

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

Nervous system

Seizure, seizure recurrence

7 DRUG INTERACTIONS

Nitrates

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

Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of sildenafil with ritonavir and other potent CYP3A inhibitors is not recommended [*see Clinical Pharmacology (12.3)*].

Other drugs that reduce blood pressure

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

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

Monitor blood pressure when co-administering blood pressure lowering drugs with sildenafil [see *Warnings and Precautions (5.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis). Because animal reproduction studies are not always predictive of human response, sildenafil should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of sildenafil, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 36%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered TID.

The primary objective of the study was to assess the effect of sildenafil on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n = 115). Administration of sildenafil did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to sildenafil remained on his/her dose of sildenafil or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose sildenafil. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients were followed for a median of 4 years (range 0.3 years to 7.0 years). Mortality during the long-term study, by originally assigned dose, is shown in Figure 6:

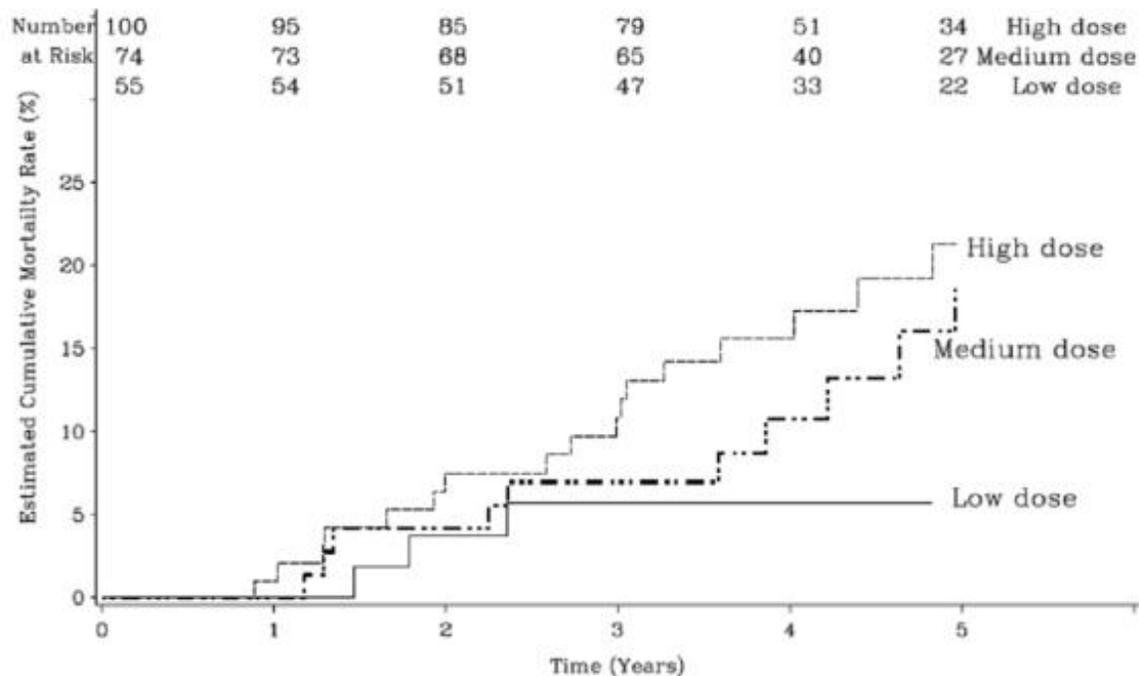


Figure 6. Kaplan-Meier Plot of Mortality by Sildenafil Dose

An increase in mortality was observed with increasing sildenafil doses. The hazard ratio for high dose compared to low dose was 3.5, $p=0.015$. Causes of death were typical of patients with PAH. Use of sildenafil, particularly chronic use, is not recommended in children.

8.5 Geriatric Use

Clinical studies of sildenafil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Clinical Pharmacology* (12.3)].

8.6 Patients with Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Renal Impairment

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

10 OVERDOSAGE

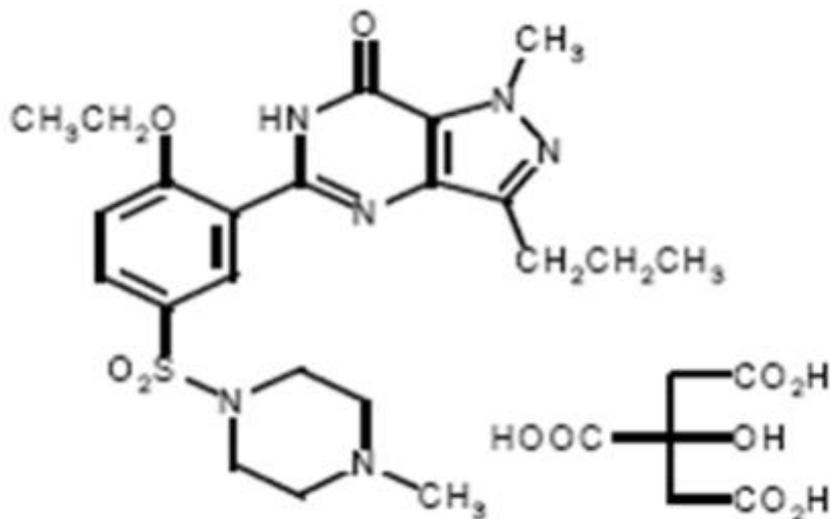
In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

11 DESCRIPTION

Sildenafil citrate, USP, phosphodiesterase-5 (PDE-5) inhibitor, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE-5). Sildenafil is also marketed as VIAGRA[®] for erectile dysfunction.

Sildenafil citrate, USP 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, USP 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.

Sildenafil Tablets: Sildenafil is formulated as white, round shaped convex film-coated tablets with 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, USP, each tablet contains the following inactive ingredients: anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, opadry II blue and opadry II white. Opadry II blue contains: polyethylene glycol 3350, polyvinyl alcohol, talc, titanium dioxide, FD&C Blue # 2 aluminum lake and FD&C Yellow # 6 aluminum lake. Opadry II white contains: polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE-5) in the smooth muscle of the pulmonary vasculature, where PDE-5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with PAH, 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 PDE-5. Its effect is more potent on PDE-5 than on other known phosphodiesterases (10-fold for PDE6, greater than 80-fold for PDE1, greater than 700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE-5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE-5 compared to PDE6, an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is

thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels [see *Clinical Pharmacology (12.2)*].

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE-5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE-5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed *in vitro*, and the mild peripheral arterial-venous dilatation *in vivo*.

12.2 Pharmacodynamics

Effects of Sildenafil on Blood Pressure

Single oral doses of sildenafil 100 mg administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8/5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different from placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg doses of sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates [see *Contraindications (4)*].

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg TID to patients with PAH, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg TID sildenafil to healthy volunteers, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 mmHg and 8.4 mmHg, respectively.

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

After chronic dosing of 80 mg TID sildenafil to patients with PAH, lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease in both of 2 mmHg).

Effects of Sildenafil 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 sildenafil on visual acuity, intraocular pressure, or pupillometry.

12.3 Pharmacokinetics

Absorption and Distribution

Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25 to 63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When sildenafil is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (V_{ss}) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism and Excretion

Sildenafil is cleared predominantly by the CYP3A (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase

selectivity profile similar to sildenafil and an *in vitro* potency for PDE-5 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 PAH, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours.

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

Population Pharmacokinetics

Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in patients with PAH. The dataset available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a significant impact on sildenafil pharmacokinetics in patients with PAH.

In patients with PAH, the average steady-state concentrations were 20 to 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 PAH compared to healthy volunteers.

Geriatric Patients

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 84% and 107% higher plasma concentrations of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy younger volunteers (18 to 45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.

Renal Impairment

In volunteers with mild ($CL_{cr} = 50$ to 80 mL/min) and moderate ($CL_{cr} = 30$ to 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} less than 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 200% and 79%, respectively, in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic Impairment

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

Drug Interaction Studies

***In vitro* studies**

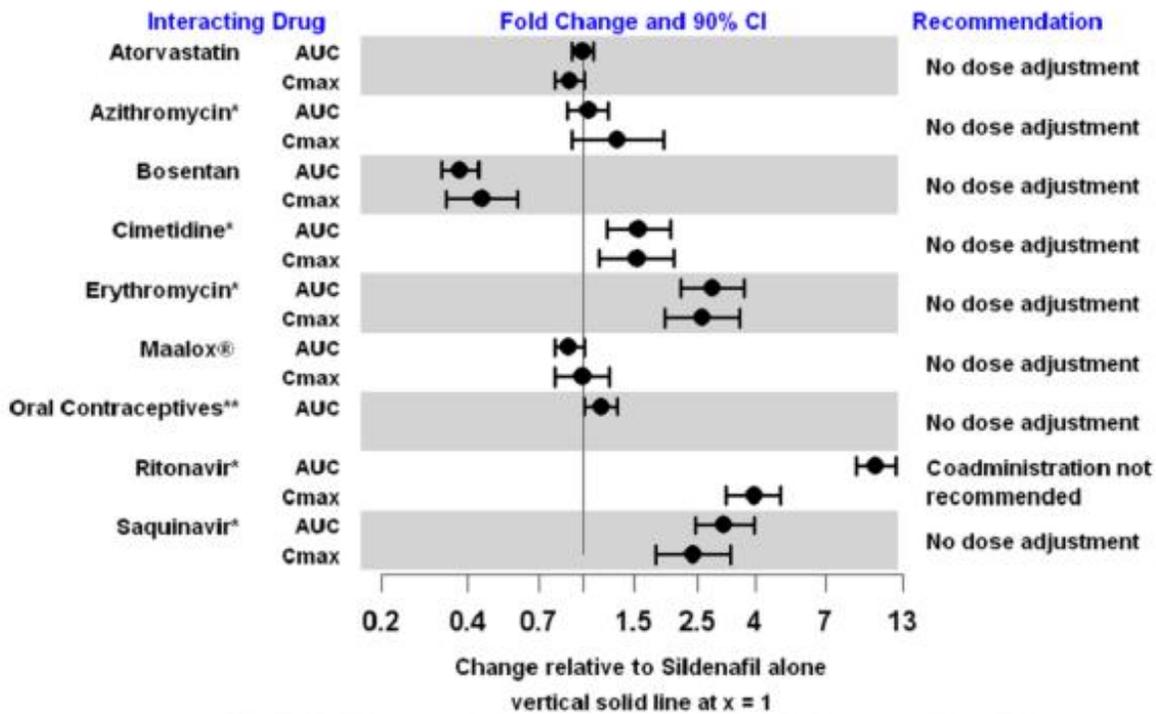
Sildenafil metabolism is principally mediated by the CYP3A (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A (IC_{50} greater than 150 μ M).

Sildenafil is not expected to affect the pharmacokinetics of compounds which are substrates of these CYP enzymes at clinically relevant concentrations.

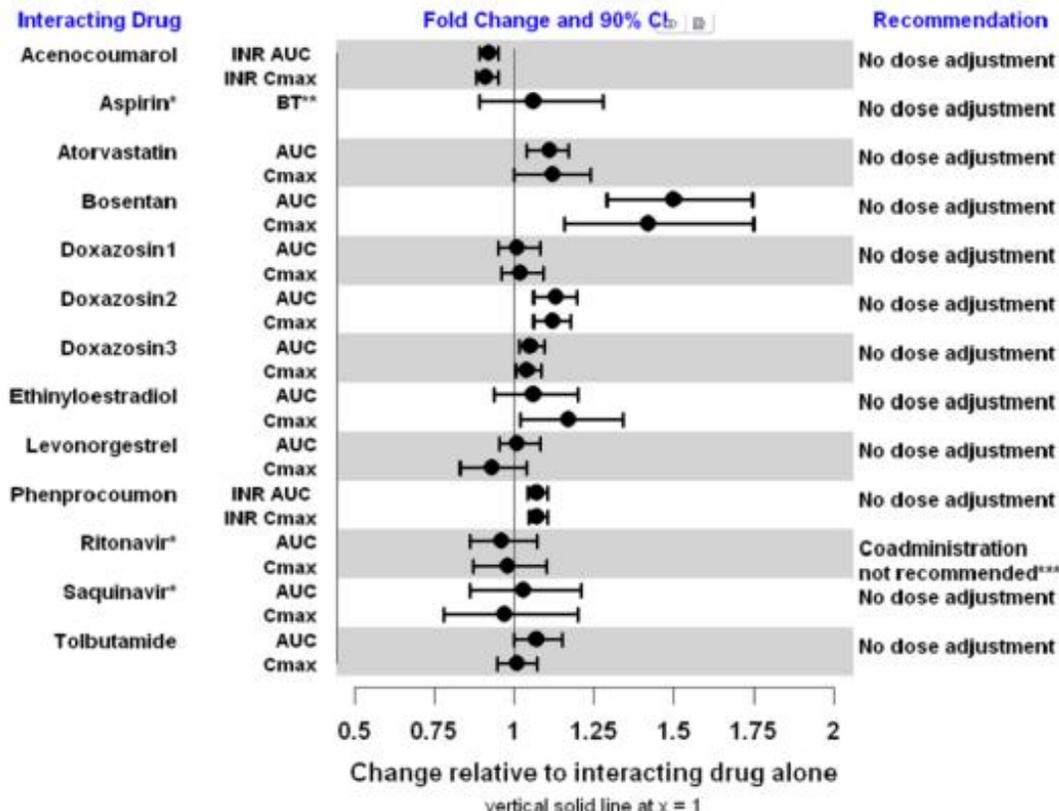
In vivo studies

The effects of other drugs on sildenafil pharmacokinetics and the effects of sildenafil on the exposure to other drugs are shown in Figure 7 and Figure 8, respectively.



* 95% CI; ** AUC accumulation ratio from Day 1 to Day 7 relative to sildenafil alone

Figure 7. Effects of Other Drugs on Sildenafil Pharmacokinetics



Doxazosin1, 25 mg; 2, 50 mg; and 3, 100 mg sildenafil; * 95% CI; ** BT = bleeding time

Figure 8. Effects of Sildenafil on Other Drugs

CYP3A Inhibitors and Beta Blockers

Population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 30% reduction in sildenafil clearance when it was co-administered with mild/moderate CYP3A inhibitors and an approximately 34% reductions in sildenafil clearance when co-administered with beta-blockers. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg TID compared to its exposure at a dose of 20 mg TID. This concentration range covers the same increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir).

CYP3A4 inducers

Population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 3-fold increase in sildenafil clearance when it was co-administered with mild CYP3A inducers, which is consistent with the effect of bosentan on sildenafil clearance in healthy volunteers. Concomitant administration of potent CYP3A inducers is expected to cause substantial decreases in plasma levels of sildenafil.

Epoprostenol

The mean reduction of sildenafil (80 mg TID) bioavailability due to co-administration of epoprostenol was 28%, resulting in about 22% lower mean average steady state concentrations. Therefore, the slight decrease of sildenafil exposure in the presence of epoprostenol is not considered clinically relevant. The effect of sildenafil on epoprostenol pharmacokinetics is not known.

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

Alcohol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

Studies of Adults with Pulmonary Arterial Hypertension

Study 1

A randomized, double-blind, placebo-controlled study of sildenafil (Study 1) was conducted in 277 patients with PAH (defined as a mean pulmonary artery pressure of greater than 25 mmHg at rest with a pulmonary capillary wedge pressure less than 15 mmHg). Patients were predominantly World Health Organization (WHO) functional classes II-III. Allowed background therapy included a combination of anticoagulants, digoxin, calcium channel blockers, diuretics, and oxygen. The use of prostacyclin analogues, endothelin receptor antagonists, and arginine supplementation were not permitted. Subjects who had failed to respond to bosentan were also excluded. Patients with left ventricular ejection fraction less than 45% or left ventricular shortening fraction less than 0.2 also were not studied.

Patients were randomized to receive placebo (n=70) or sildenafil tablets 20 mg (n = 69), 40 mg (n = 67) or 80 mg (n = 71) TID for a period of 12 weeks. They had either primary pulmonary hypertension (PPH) (63%), PAH associated with CTD (30%), or PAH following surgical repair of left-to-right congenital heart lesions (7%). The study population consisted of 25% men and 75% women with a mean age of 49 years (range: 18-81 years) and baseline 6-minute walk distance between 100 and 450 meters (mean 343).

The primary efficacy endpoint was the change from baseline at week 12 (at least 4 hours after the last dose) in the 6-minute walk distance. Placebo-corrected mean increases in walk distance of 45-50 meters were observed with all doses of sildenafil tablets. These increases were significantly different from placebo, but the sildenafil dose groups were not different from each other (see Figure 9), indicating no additional clinical benefit from doses higher than 20 mg TID. The improvement in walk distance was apparent after 4 weeks of treatment and was maintained at week 8 and week 12.

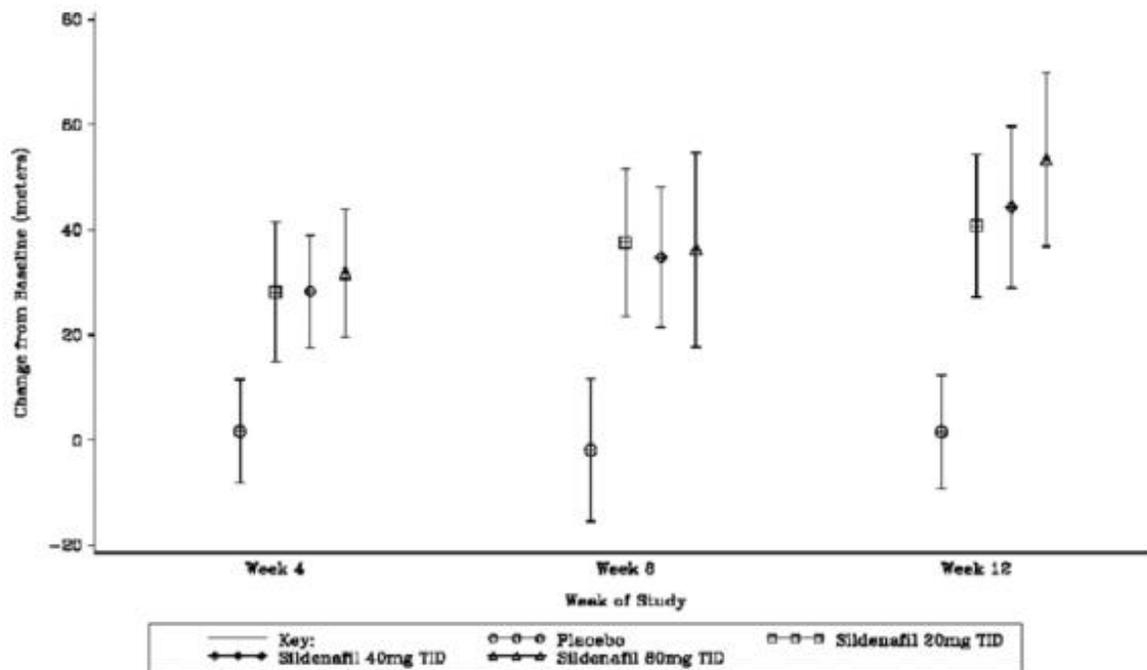


Figure 9. Change from Baseline in 6-Minute Walk Distance (meters) at Weeks 4, 8, and 12 in Study 1: Mean (95% Confidence Interval)

Figure 10 displays subgroup efficacy analyses in Study 1 for the change from baseline in 6-Minute Walk Distance at Week 12 including baseline walk distance, disease etiology, functional class, gender, age, and hemodynamic parameters.

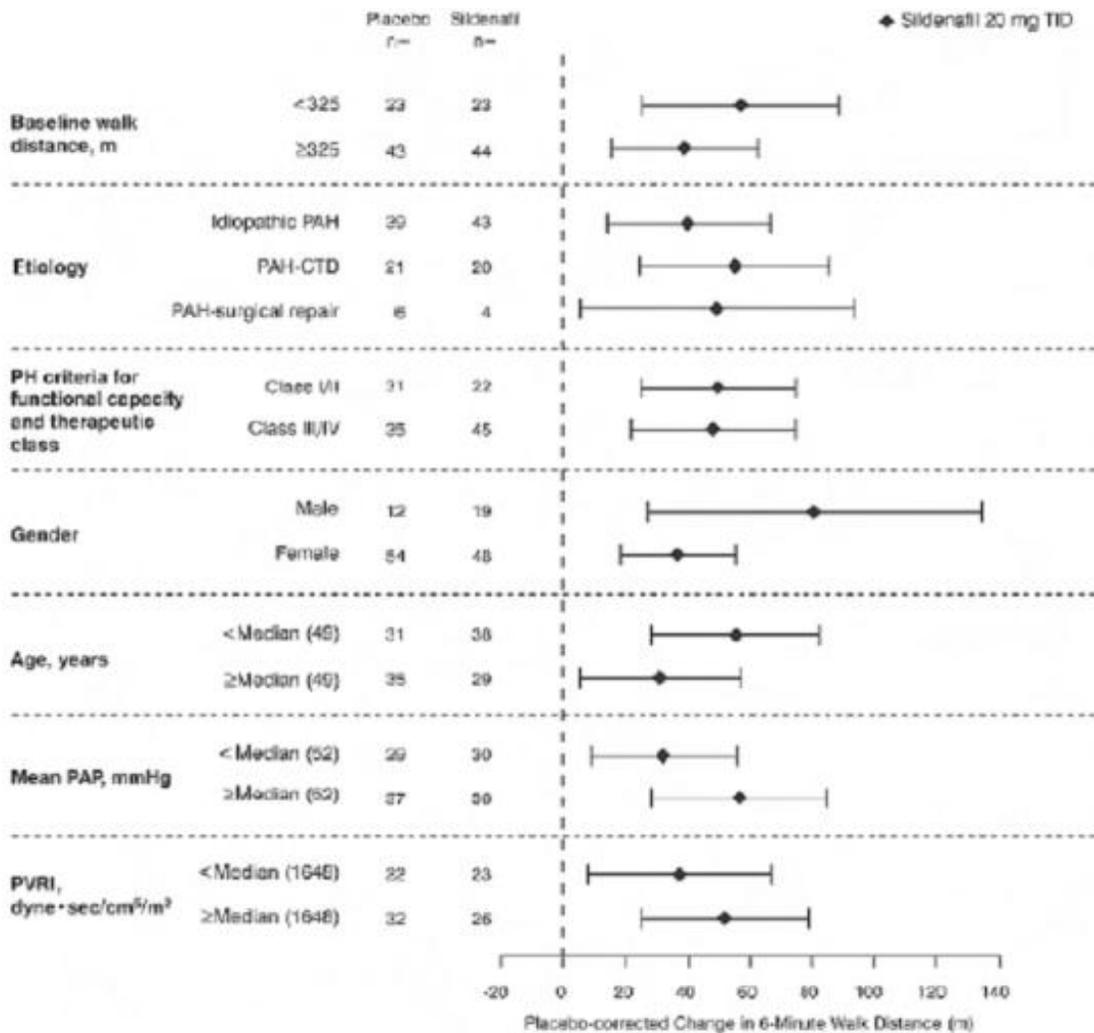


Figure 10. Placebo-Corrected Change From Baseline in 6-Minute Walk Distance (meters) at Week 12 by study subpopulation in Study 1: Mean (95% Confidence Interval)

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

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

	Placebo (n = 65)*	Sildenafil 20 mg TID (n = 65)*
mPAP (mmHg)	0.6 (-0.8, 2.0)	-2.1 (-4.3, 0.0)
PVR (dyn·s/cm⁵)	49 (-54, 153)	-122 (-217, -27)
SVR (dyn·s/cm⁵)	-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)

mPAP = mean pulmonary arterial pressure; PVR= pulmonary vascular resistance; SVR = systemic vascular resistance; RAP = right atrial pressure; CO = cardiac output; HR = heart rate

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Sildenafil tablets are supplied as white, round shaped convex film-coated tablets containing sildenafil citrate, USP equivalent to the nominally indicated amount of sildenafil as follows:

Sildenafil Tablets			
Package Configuration	Strength	NDC	Engraving on Tablet
Bottle of 90	20 mg	16714-338-01	“WPI” on one side and “3780” on other side

Recommended Storage for Sildenafil Tablets: Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Inform patients of contraindication of sildenafil tablets with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking sildenafil tablets not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking sildenafil tablets. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking sildenafil tablets. These events may be accompanied by tinnitus and dizziness.

Manufactured for: Northstar Rx LLC
Memphis, TN 38141
Toll Free: 1-800-206-7821

Manufactured by: Watson Pharma Private Ltd.
Verna, Salcette Goa 403 722 INDIA

Issued: December 2012 2002241-00

Patient Information

Sildenafil Tablets

Rx only

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

What is the most important information I should know about sildenafil tablets?

Never take sildenafil tablets with any nitrate medicines. Your blood pressure could drop quickly to an unsafe level. Nitrate medicines include:

- **Medicines that treat chest pain (angina)**
- **Nitroglycerin in any form including tablets, patches, sprays, and ointments**
- **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 are sildenafil tablets?

Sildenafil tablets are a prescription medicine used in adults to treat pulmonary arterial hypertension (PAH). With PAH, the blood pressure in your lungs is too high. Your heart has to work hard to pump blood into your lungs.

Sildenafil tablets improve the ability to exercise.

- Sildenafil tablets are not for use in children
- It is not known if sildenafil is effective for the treatment of PAH in people who are also taking a medicine called bosentan (Tracleer[®])

Sildenafil tablets contain the same medicine as VIAGRA[®] (sildenafil), which is used to treat erectile dysfunction (impotence). Do not take sildenafil tablets with VIAGRA or other PDE-5 inhibitors.

Who should not take sildenafil tablets?

Do not take sildenafil tablets if you:

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

What should I tell my doctor before taking sildenafil tablets?

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

- have heart problems such as angina (chest pain), heart failure, irregular heartbeats, or have had a heart attack
- 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 any problem with the shape of your penis or Peyronie’s disease
- have any blood cell problems such as sickle cell anemia
- have a stomach ulcer or any bleeding problems
- are pregnant or planning to become pregnant. It is not known if sildenafil could harm your unborn baby.
- are breastfeeding. It is not known if sildenafil 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. Sildenafil tablets 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 sildenafil tablets.

Especially tell your doctor if you take

- Nitrate medicines. See “**What is the most important information I should know about sildenafil tablets?**”
- Ritonavir (Norvir[®]) or other medicines used to treat HIV infection
- Ketoconazole (Nizoral[®])
- Itraconazole (Sporanox)
- High blood pressure medicine

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 sildenafil tablets?

- Take sildenafil tablets exactly as your doctor tells you.

Sildenafil tablets may be prescribed to you as

- Sildenafil tablets
 - Take a sildenafil tablet 3 times a day about 4 to 6 hours apart.
 - Take sildenafil tablets at the same times every day.
 - 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 sildenafil tablets at a time.
 - Do not change your dose or stop taking sildenafil tablets on your own. Talk to your doctor first.
 - **If you take too many sildenafil tablets, call your doctor or go to the nearest hospital emergency room.**

What are the possible side effects of sildenafil tablets?

- **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 sildenafil tablets. More shortness of breath than usual may be due to your underlying medical condition.
- **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 medicines, 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 with sildenafil tablets include:

Nosebleed, headache, upset stomach, getting red or hot in the face (flushing), trouble sleeping, as well as fever, erection increased, respiratory infection, nausea, vomiting, bronchitis, pharyngitis, runny nose, and pneumonia in children.

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 sildenafil tablets. For more information, ask your doctor or

pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store sildenafil tablets?

- Store sildenafil tablets at controlled room temperature, between 68°F to 77°F (20°C to 25°C).
- **Keep sildenafil tablets and all medicines away from children.**

General information about sildenafil tablets

Medicines are sometimes prescribed for purposes that are not in the patient leaflet. Do not use sildenafil tablets for a condition for which it was not prescribed. Do not give sildenafil tablets 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 sildenafil tablets. If you would like more information about sildenafil tablets talk with your doctor. You can ask your doctor or pharmacist for information about sildenafil tablets that is written for health professionals. For more information you can call Northstar Rx LLC at 1-800-206-7821.

What are the ingredients in sildenafil tablets?

Active ingredients: sildenafil citrate, USP

Inactive ingredients: anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, opadry II blue and opadry II white. Opadry II blue contains: polyethylene glycol 3350, polyvinyl alcohol, talc, titanium dioxide, FD&C Blue # 2 aluminum lake and FD&C Yellow # 6 aluminum lake. Opadry II white contains: polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration

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Issued: December 2012 2002241-00

Principal Display Panel

Rx Only

NDC 16714-338-01

Sildenafil

Tablets 20 mg

PHARMACIST: PLEASE DISPENSE WITH THE PATIENT INFORMATION SHEET.

90 Tablets

NorthStar

Rx only

Rx Only

NDC 16714-338-01

Sildenafil

Tablets 20 mg

90 tablets

NORTHSTAR_X

PHARMACIST: PLEASE DISPENSE WITH THE PATIENT INFORMATION SHEET.

Each film-coated tablet contains: Sildenafil citrate, USP equivalent to 20 mg sildenafil.

Usual dosage: See accompanying prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in tight containers.

Mfd for: Northstar Rx LLC
 Memphis, TN 38141
 Toll Free: 1-800-206-7821

Mfd by: Watson Pharma Private Limited
 Verna, Salcette Goa 403 722 INDIA

Code No. G0/DRUGS/741 112/12
2002240-00



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SILDENAFIL

sildenafil citrate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:16714-338
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SILDENAFIL CITRATE (SILDENAFIL)	SILDENAFIL	20 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM PHOSPHATE, DIBASIC, ANHYDROUS	
CROSCARMELOSE SODIUM	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYETHYLENE GLYCOL 3350	
POLYVINYL ALCOHOL	
TALC	
TITANIUM DIOXIDE	
FD&C BLUE NO. 2	
FD&C YELLOW NO. 6	
ALUMINUM OXIDE	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND (Convex)	Size	7mm
Flavor		Imprint Code	WPI;3780
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16714-338-01	90 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202503	02/26/2013	

Labeler - Northstar RxLLC (830546433)

Establishment

Name	Address	ID/FEI	Business Operations
Watson Laboratories, Inc. - Florida		014759176	LABEL(16714-338), PACK(16714-338)

Establishment

Name	Address	ID/FEI	Business Operations
Watson Pharma Private Limited		677605709	ANALYSIS(16714-338), LABEL(16714-338), MANUFACTURE(16714-338), PACK(16714-338)

Revised: 12/2012

Northstar RxLLC