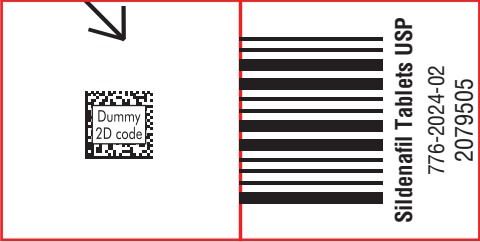


2D Data Matrix to be printed with serial number on each leaflet. The number should not be repeated

Note: Position of the pharma code and product name will change as per the folding machine feasibility



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-----	
Indications and Usage (1)	1/2023
Dosage and Administration (2.1)	1/2023
-----INDICATIONS AND USAGE-----	
Adults Sildenafil tablets are a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening. (1)	
-----DOSAGE AND ADMINISTRATION-----	
• Adults: 20 mg three times a day. (2.1)	
-----DOSAGE FORMS AND STRENGTHS-----	
• Tablets: 20 mg (3)	
-----CONTRAINDICATIONS-----	
• Use with organic nitrates or riociguat. (4) • History of hypersensitivity reaction to sildenafil or any component of the tablet. (4)	
-----WARNINGS AND PRECAUTIONS-----	
• Vasodilation effects may be more common in patients with hypotension or on antihypertensive therapy. (5.1)	

FULL PRESCRIBING INFORMATION: CONTENTS *

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- Use in pulmonary veno-occlusive disease (PVOD) may cause pulmonary edema and is not recommended. (5.2)
 - Hearing or visual impairment: Seek medical attention if sudden decrease or loss of vision or hearing occurs. (5.4, 5.5)
 - Pulmonary hypertension (PH) secondary to sickle cell disease: Sildenafil may cause serious vaso-occlusive crises. (5.8)
- ADVERSE REACTIONS-----
- Adults: Headache, dyspepsia, flushing, pain in limb, myalgia, back pain and diarrhea. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- DRUG INTERACTIONS-----
- Use with strong CYP3A inhibitors: Not recommended. (7, 12.3)
 - Concomitant PDE-5 inhibitors: Avoid use with Viagra® or other PDE-5 inhibitors. (5.6)

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

Pediatric use information is approved for Viatris Specialty LLC's, REVATIO (sildenafil) tablets. However, due to Viatris Specialty LLC's marketing exclusivity rights, this drug product is not labeled with that information.

Revised: 02/2024

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*Sections or subsections omitted from the full prescribing information are not listed.

Table 1. Most Common Adverse Reactions in Patients Treated with Sildenafil 20 mg, 40 mg, 80 mg and Placebo three times per day in SUPER-1 (More Frequent in Sildenafil -Treated Patients than Placebo-Treated Patients)

	Sildenafil 20 mg (n = 69)	Sildenafil 40 mg (n = 67)	Sildenafil 80 mg (n = 71)	Placebo (n = 70)
Headache	46%	42%	49%	39%
Flushing	10%	9%	16%	4%
Pain in Limb	7%	15%	9%	6%
Myalgia	7%	6%	14%	4%
Back Pain	13%	13%	9%	11%
Dyspepsia	13%	8%	13%	7%
Diarrhea	9%	12%	10%	6%

In a placebo-controlled fixed dose titration study (PACES-1) of sildenafil (starting with recommended dose of 20 mg and increased to 40 mg and then 80 mg all three times a day) as an adjunct to intravenous epoprostenol in patients with PAH, no new safety issues were identified except for edema, which occurred in 25% of subjects in the combined sildenafil+ epoprostenol group compared with 13% of subjects in the epoprostenol group [See Clinical Studies (14)].

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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

Ophthalmologic

NAION [See Warnings and Precautions (5.4), Patient Counseling Information (17)].

7 DRUG INTERACTIONS

Nitrates

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

Strong CYP3A Inhibitors

Concomitant use of sildenafil with strong CYP3A inhibitors is not recommended [See Clinical Pharmacology (12.3)].

Moderate-to-Strong CYP3A Inducers

Concomitant use of sildenafil with moderate-to-strong CYP3A inducers (such as bosentan) decreases the sildenafil exposure. Dose up-titration of sildenafil may be needed when initiating treatment with moderate-to-strong CYP3A inducers. Reduce the dose of sildenafil to 20 mg three times a day when discontinuing treatment with moderate-to-strong CYP3A inducers [See Clinical Pharmacology (12.3) and Clinical Studies (14)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data from randomized controlled trials, case-controlled trials, and case series do not report a clear association with sildenafil and major birth defects, miscarriage, or adverse maternal or fetal outcomes when sildenafil is used during pregnancy. There are risks to the mother and fetus from untreated pulmonary arterial hypertension [See Clinical Considerations]. Animal reproduction studies conducted with sildenafil showed no evidence of embryo-fetal toxicity or teratogenicity at doses up to 32- and 65-times the recommended human dose (RHD) of 20 mg three times a day in rats and rabbits, respectively [See Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women with untreated pulmonary arterial hypertension are at risk for heart failure, stroke, preterm delivery, and maternal and fetal death.

Data

Animal Data

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 65-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. 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).

8.2 Lactation

Risk Summary

Limited published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of sildenafil to an infant during lactation.

8.4 Pediatric Use

The safety and effectiveness of sildenafil have not been established in pediatric patients younger than 1 year of age.

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8.5 Geriatric Use

Clinical studies of sildenafil did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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

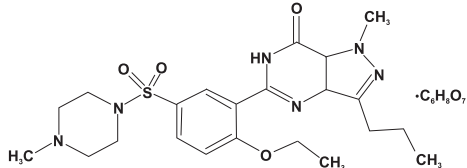
In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

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 tablet, 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 slightly soluble in methanol and a molecular weight of 666.70.

Sildenafil tablets are formulated as white to off white, film coated, round tablets for oral administration. Each tablet contains sildenafil citrate, USP equivalent to 20 mg of sildenafil. In addition to the active ingredient, sildenafil citrate, USP, each tablet contains the following inactive ingredients: croscarmellose sodium, dibasic calcium phosphate anhydrous, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sildenafil is an inhibitor of cGMP specific 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, vasodilation in the systemic circulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, 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 times as potent for PDE5 compared to PDE6, an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels [See Clinical Pharmacology (12.2)].

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

12.2 Pharmacodynamics

Effects of Sildenafil on Hemodynamic Measures

Adults

Patients on all sildenafil doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo in a study with no background vasodilators [see SUPER-1 in Clinical Studies (14)]. Data on other hemodynamic measures for the sildenafil 20 mg three times a day and placebo dosing regimens is displayed in Table 2. The relationship between these effects and improvements in 6-minute walk distance is unknown.

Table 2. Changes from Baseline in Hemodynamic Parameters at Week 12 [mean (95% CI)] for the Sildenafil 20 mg Three Times a Day and Placebo Group

	Placebo (n = 65)*	Sildenafil 20 mg (n = 65)*
mPAP (mmHg)	0.6 (-0.8, 2)	-2.1 (-4.3, 0.0)
PVR (dyn.s/cm ²)	49 (-54, 153)	-122 (-217, -27)
SVR (dyn.s/cm ²)	-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.

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 electrocardiogram (ECG). After chronic dosing of 80 mg three times a day to patients with PAH, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg three times a day sildenafil to healthy volunteers, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9 mmHg and 8.4 mmHg, respectively.

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

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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.

Bioequivalence was established between the 20 mg tablet and the 10 mg/mL oral suspension when administered as a 20 mg single oral dose of sildenafil (as citrate).

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_{max} 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.

Pediatric Patients


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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} = 50–80 mL/min) and moderate (CL_{cr} = 30–49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CL_{cr} 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 patients with severe renal impairment compared to patients with normal renal function.

Artwork information			
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Printing Colours (01)	Black		
Others: Note: Position, Height of the pharma code are tentative, it can be changed based on folding size.			

Version: 03

