

SILDENAFIL- sildenafil tablet, film coated
Northwind Pharmaceuticals, LLC

SILDENAFIL

INDICATIONS & USAGE

Sildenafil tablets are indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when sildenafil tablets were added to background epoprostenol therapy [see Clinical Studies (14)].

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use

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

DOSAGE & ADMINISTRATION

The recommended dose of sildenafil tablets is 20 mg three times a day (TID). Administer sildenafil tablet 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.

CONTRAINDICATIONS

Sildenafil citrate 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.

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 citrate dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of sildenafil citrate, particularly chronic use, is not recommended in children. [see Use in Specific Populations (8.4)].

5.2 Hypotension

Sildenafil citrate has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing sildenafil tablets, 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 citrate.

5.3 Worsening Pulmonary Vascular Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of sildenafil citrate to patients with veno-occlusive disease, administration of sildenafil citrate to such patients is not recommended. Should signs of pulmonary edema occur when sildenafil citrate 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 citrate 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 citrate. 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 citrate in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe sildenafil citrate 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 citrate. 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 citrate, 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 citrate.

5.7 Combination with other PDE-5 inhibitors

Sildenafil is also marketed as sildenafil citrate tablets, 25 mg, 50 mg and 100 mg. The safety and efficacy of combinations of sildenafil tablets, 20 mg with sildenafil citrate tablets, 25 mg, 50 mg and 100 mg or other PDE-5 inhibitors have not been studied. Inform patients taking sildenafil tablets, 20 mg not to take sildenafil citrate tablets, 25 mg, 50 mg and 100 mg or other PDE-5 inhibitors.

5.8 Priapism

Use sildenafil citrate 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 citrate than by those randomized to placebo. The effectiveness and safety of sildenafil citrate in the treatment of PAH secondary to sickle cell anemia has not been established.

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

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

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<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bc081f2-399d-43fa-9e0f-9f8df0118e99>

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.

In a placebo-controlled fixed dose titration study (Study 2) of sildenafil citrate (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in patients with PAH, the adverse reactions that were more frequent in the sildenafil citrate + epoprostenol group than in the epoprostenol group (greater than 6% difference).

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

DRUG INTERACTIONS

Nitrates

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

Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of sildenafil citrate 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 citrate [see Warnings and Precautions (5.2)].

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 citrate should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

The safety and efficacy of sildenafil citrate 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 citrate 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 citrate, 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 citrate on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n = 115). Administration of sildenafil citrate 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 citrate remained on his/her dose of sildenafil citrate or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose sildenafil citrate. 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).

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<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bc081f2-399d-43fa-9e0f-9f8df0118e99>

An increase in mortality was observed with increasing sildenafil citrate 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 citrate, particularly chronic use, is not recommended in children.

8.5 Geriatric Use

Clinical studies of sildenafil citrate 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)].

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.

DESCRIPTION

Sildenafil tablets, 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 sildenafil citrate tablets, 25 mg, 50 mg and 100 mg for erectile dysfunction.

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate.

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.

Sildenafil Tablets: Sildenafil citrate is formulated as white, film-coated round tablets with 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: croscarmellose sodium, dibasic calcium phosphate anhydrous, hypromellose, microcrystalline cellulose, sodium stearyl fumarate, titanium dioxide and triacetin.

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, vasodilation 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 Citrate 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 Citrate 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 citrate on visual acuity, intraocular pressure, or pupillometry.

12.3 Pharmacokinetics

Absorption and Distribution

Sildenafil citrate is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25-63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When sildenafil citrate 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 20-50% 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 (18-45 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 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 (IC₅₀ greater than 150 μM).

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

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<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bc081f2-399d-43fa-9e0f-9f8df0118e99>

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%.

NONCLINICAL TOXICOLOGY

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.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Inform patients of contraindication of sildenafil citrate with regular and/or intermittent use of organic nitrates.

Inform patients that sildenafil is also marketed as sildenafil citrate tablets, 25 mg, 50 mg and 100 mg for erectile dysfunction. Advise patients taking sildenafil tablets, 20 mg not to take sildenafil citrate tablets, 25 mg, 50 mg and 100 mg 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.

Sildenafil Tablets

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 and can slow down worsening changes in your physical condition.

Sildenafil tablets are not for use in children

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

Sildenafil tablet contains the same medicine as sildenafil citrate tablets, 25 mg, 50 mg and 100 mg, which are used to treat erectile dysfunction (impotence). Do not take sildenafil tablets, 20 mg with sildenafil citrate tablets, 25 mg, 50 mg and 100 mg or other PDE-5 inhibitors.

Who should not take sildenafil tablet?

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 sickle cell anemia

have a stomach ulcer or any bleeding problems

are pregnant or planning to become pregnant. It is not known if sildenafil tablets could harm your unborn baby.

are breastfeeding. It is not known if sildenafil citrate 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 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 much 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 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

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 Call 1-269-544-2299.

What are the ingredients in sildenafil tablets?

Sildenafil Tablets

Active ingredients: sildenafil citrate

Inactive ingredients: croscarmellose sodium, dibasic calcium phosphate anhydrous, hypromellose, microcrystalline cellulose, sodium stearyl fumarate, titanium dioxide and triacetin.

This product's label may have been updated. For current full prescribing information, please visit www.torrentpharma.com

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC: 51655-131-53

MFG: 13668-185-90

Sildenafil 20 MG

10 Tablets

Rx Only

Lot#:

Exp. Date:

Each film-coated tablet contains sildenafil citrate equivalent to 20 mg of sildenafil

Dosage: See prescriber's instructions

Store between 68-77 degrees F.

Keep out of the reach of children.

Medication guide is found at www.fda.gov/drugs/drugsafety/ucm085729

Mfg. by Torrent Pharmaceuticals Ltd. Indred 362721 India

Mfg for Torrent Pharma Inc. Kalamazoo MI 49009 Lot#

Repackaged by Northwind Pharmaceuticals, Indianapolis, IN 46256

NDC: 51655-131-53 LCN# 01
MFG: 13668-185-90 Rev. 2

Sildenafil 20MG
10 Tablets
NDC: 51655-131-53
MFG: 13668-185-90
Lot #: NW89450001
Exp. Date: 09/2015

Sildenafil 20MG
10 Tablets
NDC: 51655-131-53
MFG: 13668-185-90
Lot #: NW89450001
Exp. Date: 09/2015

Sildenafil 20MG
10 Tablets
NDC: 51655-131-53
MFG: 13668-185-90
Lot #: NW89450001
Exp. Date: 09/2015

Sildenafil 20MG
10 Tablets
NDC: 51655-131-53
MFG: 13668-185-90
Lot #: NW89450001
Exp. Date: 09/2015

Sildenafil 20MG
10 Tablets
Rx Only

Lot #: NW89450001
Exp. Date: 09/2015

Each film-coated tablet contains sildenafil citrate equivalent to 20 mg of sildenafil
Dosage: See prescriber's instructions
Store between 68-77 degrees F.

Keep out of the reach of children.

Medication guide is found at www.fda.gov/drugs/drugsafety/ucm085729
Mfg. by Torrent Pharmaceuticals Ltd., Indrad 362721 India
Mfg. for Torrent Pharma Inc. Kalamazoo, MI 49009 Lot# BT723002
Repackaged By: Northwind Pharmaceuticals, Indianapolis, IN 46256

NDC: 51655-131-20

MFG: 13668-185-90

Sildenafil 20 MG

20 Tablets

Rx Only

Lot#:

Exp. Date:

Each film-coated tablet contains sildenafil citrate equivalent to 20 mg of sildenafil

Dosage: See prescriber's instructions

Store between 68-77 degrees F.

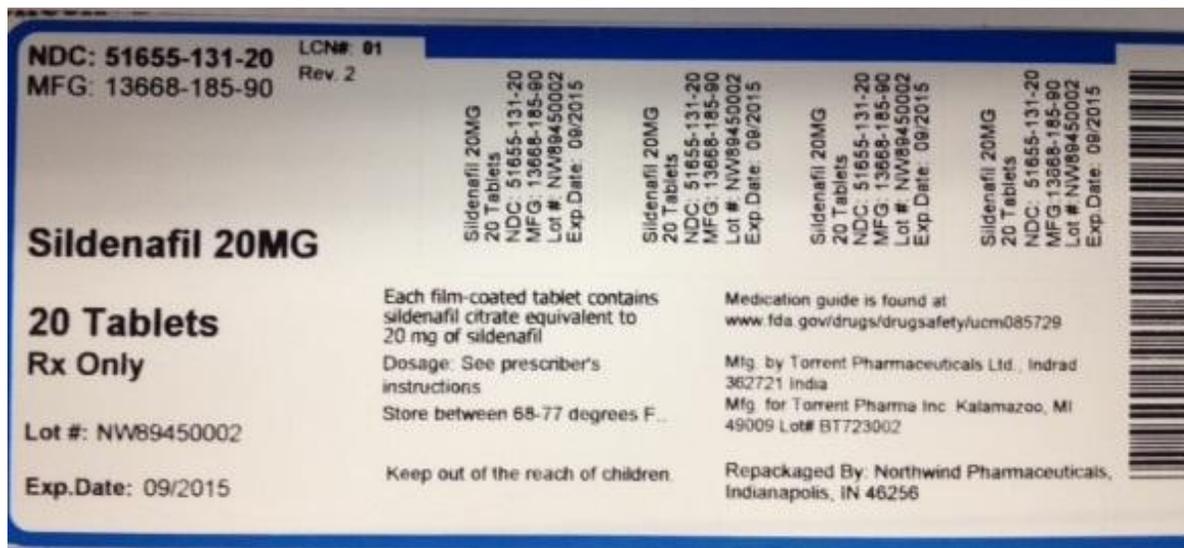
Keep out of the reach of children.

Medication guide is found at www.fda.gov/drugs/drugsafety/ucm085729

Mfg. by Torrent Pharmaceuticals Ltd. Indred 362721 India

Mfg for Torrent Pharma Inc. Kalamazoo MI 49009 Lot#

Repackaged by Northwind Pharmaceuticals, Indianapolis, IN 46256



SILDENAFIL

sildenafil tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51655-131(NDC:13668-185)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SILDENAFIL CITRATE (UNII: BW9B0ZE037) (SILDENAFIL - UNII:3M7OB98Y7H)	SILDENAFIL	20 mg

Product Characteristics

Color	white	Score	no score
Shape	ROUND	Size	7mm
Flavor		Imprint Code	85
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51655-131-53	10 in 1 BOTTLE, DISPENSING		
2	NDC:51655-131-20	20 in 1 BOTTLE, DISPENSING		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091479	11/06/2014	

Labeler - Northwind Pharmaceuticals, LLC (036986393)

Registrant - Northwind Pharmaceuticals, LLC (036986393)

Establishment

Name	Address	ID/FEI	Business Operations
Northwind Pharmaceuticals, LLC		036986393	repack(51655-131)

Revised: 11/2014

Northwind Pharmaceuticals, LLC