130.00 mm

220.00 mm

SILDENAFIL CITRATE

50 mg Orally Disintegrating Strip

Phosphodiesterase-5 (PDE5) inhibitor

℞

FORMULATIONS
Each orally disintegrating strip contains:
Sildenafil citrate, USP ..... 50 mg

PRODUCT DESCRIPTION
Orally disintegrating strip
Blue colored rectangular opaque, non-sticky orally disintegrating strip

PHARMACODYNAMICS
Pharmacodynamic Properties:
Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction.
ATC Code: G04B E03.

Mechanism of action
Sildenafil inhibits the cGMP-specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum located around the penis. Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) by sildenafil enhances erectile function by increasing the amount of cGMP.

Clinical efficacy and safety
Erections are controlled by the parasympathetic nervous system. Upon sexual stimulation, a decrease in vascular resistance is mediated by acetylcholine and nitric oxide resulting in vasodilation. The hemodynamic mechanism of an erection is comprised of five stages. During the latent stage, arterial and carvernous smooth muscle relaxation occurs. Vasodilation results in high levels of blood flow causing the penis to grow to its full size. This stage is called tumescence. During the full-erection stage, blood flow fills penis sinusoids and outflow is restricted. This is followed by the rigid-erection phase during which the cavernous muscles contract causing the penis to become rigid. Little blood flow occurs during this stage. During the final stage, detumescence, the cavernous muscles relax and blood flows out of the penis. Erectile dysfunction may occur when there is insufficient blood supply to the penis or when the penis is unable to prevent outflow of blood from the penis. Sildenafil is a specific inhibitor of PDE5, an enzyme responsible for the breakdown of cGMP to 5'-GMP. Increased levels of cGMP stimulate vasodilation and facilitate the generation and maintenance of erections. These vasodilatory effects also help decrease symptoms of PAH. Sildenafil also exhibits some activity against PDE6 (10 times less potency compared to PDE5), a PDE isoform found predmoninantly in the retina. This activity is responsible for the blue tinged vision experienced by users of sildenafil.

PHARMACOKINETICS
Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (range 25–63%). Its pharmacokinetics is dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. The concomitant use of potent cytochrome P450 3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil. Both sildenafil and the metabolite have terminal half-lives of about 4 hours.

Absorption and Distribution
Sildenafil is rapidly absorbed. 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 Tmax of 60 minutes and a mean reduction in Cmax of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion
Sildenafil is cleared predominantly by the CYP3A4 (major route) and 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 PDE selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. 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.

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

Special populations
Elderly
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal Insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and Cmax of the N-desmethyl metabolite increased up to 126% and up to 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance < 30 mL/min), sildenafil clearance was reduced, resulting in mean increases in AUC and Cmax of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased by 200% and 79% respectively.

Hepatic Insufficiency
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

INDICATIONS
- Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
- In order for Sildenafil to be effective, sexual stimulation is required.

DOSAGE AND ADMINISTRATION
Dosing of orally disintegrating strips as follows:
Use in adults: The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

Special Populations
Use in the elderly: Dosage adjustments are not required in elderly patients.
Use in patients with impaired renal function: The dosing recommendations described in 'Use in adults' apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 mL/min).

Since Sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired hepatic function: Since Sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis), a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

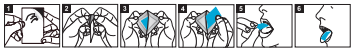
Use in children and adolescents: Sildenafil is not indicated for individuals below 18 years of age.

Use in patients using other medicines: With the exception of ritonavir for which co-administration with Sildenafil is not advised a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors.
In order to minimize the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating Sildenafil treatment. In addition, initiation of Sildenafil at a dose of 25 mg should be considered.

Direction for use:

METHOD OF ADMINISTRATION
- For oral use.
- Placed over the tongue, dissolved and swallowed orally.

DIRECTION FOR USE



CONTRAINDICATIONS
Sildenafil is contraindicated in following conditions:

Hypersensitivity to the active substance.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, Sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

Agents for the treatment of erectile dysfunction, including Sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

Sildenafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

WARNING AND PRECAUTIONS
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

Sildenafil potentiates the hypotensive effect of nitrates.

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of Sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of Sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

130.00 mm

220.00 mm

Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia).

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Visual defects and cases of non-arteritic anterior ischemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking Sildenafil and consult a physician immediately.

Co-administration of sildenafil with ritonavir is not advised.

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

Studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside in vitro. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, sildenafil should be administered to these patients only after careful benefit-risk assessment.

Sildenafil is not indicated for use by women.

UNDESIRABLE EFFECTS
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Not known (cannot be estimated from the available data)
Very common : Headache
Common: Dizziness, Visual disorders, Visual colour distortion, Vision blurred, Flushing, Hot Flush, Nasal congestion, Dyspepsia, Nausea.
Uncommon: Rhinitis, Hypersensitivity reactions, Somnolence, Hypoaesthesia, Eye pain, Lacrimation disorder, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivis, Vertigo, Tinnitus, Hypertension, Hypotension, Palpitations, Tachycardia, Epistaxis, Sinus congestion, Gastro-oesophageal reflux disease, Vomiting, Abdominal pain upper, Dry mouth, Rash, Haematuria, Chest pain, Fatigue, Feeling hot, Heart rate increased.
Rare : Cerebrovascular accident, Transient ischaemic attack, Seizure, Seizure recurrence Syncope, Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discolouration, Deafness, Sudden cardiac death, Myocardial infarction, Ventricular arrhythmia, Atrial fibrillation, Unstable angina, Throat tightness, Nasal oedema, Nasal dryness, Hypoaesthesia oral, Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Penile haemorrhage, Priapism, Haematospermia, Erection increased, Irritability.

INTERACTIONS WITH OTHER MEDICAMENTS
Effects of other medicinal products on sildenafil
In vitro studies: Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

In vivo studies: Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin and cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100 mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg twice daily. for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max}, t_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

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

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.

Effects of sildenafil on other medicinal products
In vitro studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} > 150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that Sildenafil will alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies: Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In three specific drug - drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mm Hg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.

Sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

PREGNANCY AND LACTATION
Sildenafil is not indicated for use by women.
There are no adequate and well-controlled studies in pregnant or breastfeeding women.

OVERDOSE AND TREATMENT
Doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was 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.

STORAGE CONDITIONS

- Store at temperatures not exceeding 30°C, protect from light and moisture.
- Keep the product out of sight and reach of children.

AVAILABILITY
- Dosage Form: Orally disintegrating strip
- Packaging:
  - Each strip packed in aluminum sachet and such 10 sachets pack in carton (10 x 1 Strip)

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab, Inc. at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

Manufactured by:
ZIM LABORATORIES LIMITED
B-21/22 MIDC Area, Kalmeshwar, Nagpur 441501
Maharashtra State, India

Imported & Distributed by:
ONESOURCE PHARMA SOLUTIONS, INC.
No. 132 Pioneer St., Mandaluyong City, Philippines

REGISTRATION NUMBER: DRP-_____
DATE OF FIRST AUTHORIZATION: _____
DATE OF REVISION OF THE PACKAGE INSERT: _____