℞ GIAGRA 25, 50 & 100

Sildenafil Citrate Tablets 25, 50 & 100 mg

GIAGRA 25 (Sildenafil Citrate Tablets 25 mg)

Description: Blue colored round, biconvex, film coated tablets, debossed with 124 on one side and J on the other side.

Each film coated tablets contains Sildenafil Citrate 35.12mg is equivalent to Sildenafil 25mg

GIAGRA 50 (Sildenafil Citrate Tablets 50 mg)

Description: Blue colored round, biconvex, scored film coated tablets, debossed with 125 on one side and J on the other side with score line.

Each film coated tablets contains Sildenafil Citrate 70.24mg is equivalent to Sildenafil 50mg

GIAGRA 100 (Sildenafil Citrate Tablets 100 mg)

Description: Blue colored round, biconvex, scored film coated tablets, debossed with 126 on one side and J on the other side with score line.

Each film coated tablets contains Sildenafil Citrate 140.48mg is equivalent to Sildenafil 100mg

Dosage forms: Tablet

Pharmacodynamics

Mechanism of action

The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum.

When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

In vitro, sildenafil is found to be selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE5, > 80-fold for PDE1, > 700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PSE11). The approximately 4,000-fold selectively for PDE5 versus PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina which is 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.

In addition to human corpus cavernosum smooth muscle, PDE5 is also found in lower concentrations in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by slidenafil may be the basis for the enhanced platelet antiaggregatory activity of nitric oxide observed in vitro, an inhibition of platelet thrombus formation in vivo and peripheral arterial-venous dilatation in vivo.

Pharmacokinetics

Slidenafil is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Its pharmacokinetics is dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and isconverted 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 slidenafil. 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 105L, 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.

Less than 0.001% of the administered dose may appear in the semen after 90 minutes of sildenafil administration.

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 Ndesmethylation 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).

Pharmacokinetics in Special Populations Elderly: Healthy elderly (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in younger (18-45 years).

Hepatic impairment: In hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance is reduced, resulting in increases in AUC (84%) and C_{max} (47%).

Renal impairment: The pharmacokinetics of sildenafil 50mg is not altered in case of mild (CL_{cr}=50-80 ml/min) and moderate (CL_{cr}=30-49 ml/min) renal impairment. In severe (CLcr ≤ 30 ml/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max}.

Indications

SILDENAFIL are indicated for the treatment of 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.

Route of administration

Oral.

Recommended Dose

Adults

The recommended dose is 50mg taken, as needed, approximately 1 hour before sexual activity. Based on effectiveness and tolerance, the dose may be increased to a maximum recommended dose of 100mg or decreased to 25mg. the maximum recommended daily dose is 100mg. the maximum recommended dosing frequency is once per day.

Elderly

Dosage adjustments are not required in elderly patients.

Children

SILDENAFIL are not indicated for use in children (< 18 years).

Patients with impaired renal function

Dosage adjustments are not required in 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.

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.

Patients using other medicines

Given the extent of the interaction with patients receiving concomitant therapy with ritonavir, it is recommended not to exceed a maximum single dose of 25mg sildenafil in a 48-hr period. A starting dose of 25mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors e.g., erythromycin, saquinavir, ketoconazole, itraconazole.

Warning and Precautions

Precautions

General

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Before prescribing sildenafil, it is important to note the following:

Caution is advised when Phosphodiesterase Type 5 (PDE5) inhibitors are coadministered with alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to sympathy hypotension (e.g. dizziness, lightheadedness, fainting).

Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose.
- In those patients already taking an optimized dose of a PDE5 inhibitor, alphablocker therapy should be initiated at the lowest dose. Stepwise increase in alphablocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other antihypertensive drugs.

Sildenafil has systemic vasodilator properties and may augment the blood pressure lowering effect of other anti-hypertensive medications. Mean additional blood pressure reductions of 8 mmHg systolic and 7 mmHg diastolic were noted when amlodipine, 5 mg or 10 mg, and sildenafil, 100 mg were orally used concomitantly in hypertensive patients.

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

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 reported. Therefore, the use of such combinations is not recommended.

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. *In vitro* sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor).

Information for patients

Physicians should discuss with patients the contraindication of sildenafil with regular and/or intermittent use of organic nitrates.

Physicians should advise patients of the potential for sildenafil to augment the blood pressure lowering effect of alpha-blockers and anti-hypertensive medications. Concomitant administration of sildenafil and an alpha-blocker may lead to symptomatic hypotension in some patients. Therefore, when slidenafil is co-administered with alphablockers, patients should be stable on alpha-blocker therapy prior to initiating slidenafil treatment and slidenafil should be initiated at the lowest dose.

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (e.g. angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

Physicians should advise patients to stop use of all PDE5 inhibitors, including sildenafil, and seek medical attention in the event of a sudden loss of vision in one or both eyes.

Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all pDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION inn individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors.

Physician should advise patients to stop taking PDE5 inhibitors, including sildenafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to intake of PDE5 inhibitors, including sildenafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors.

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of sildenafil. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result. The use of sildenafil offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

Warning

There is potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including sildenafil, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

Sildenafil has systemic vasodilator properties that resulted in transient decreases in supine blood pressure (mean maximum decrease of 8.4/5.5 mmHg). While this normally would be expected to be of little consequence in most patients, prior to prescribing sildenafil, physicians should carefully considered whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilator effects, especially in combination with sexual activity.

Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators including sildenafil – those with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic sub aortic stenosis) and those with severely impaired autonomic control of blood pressure.

There is no safety or efficacy data of sildenafil reported in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (BP < 90/50) or hypertension (BP > 170/110);
- Patients with cardiac failure or coronary artery disease causing unstable angina;
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of sildenafil. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

The serum concentrations of sildenafil increases substantially (11-fold increase in AUC) on concomitant administration of the protease inhibitor ritonavir. If sildenafil is prescribed to patients taking ritonavir, caution should be used. Data exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at higher levels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported with high doses of sildenafil (200-800 mg). To decrease the chance of adverse events in patients taking ritonavir, a decrease in sildenafil dosage is recommended.

Contraindications

SILDENAFIL are contraindicated in patients with a known hypersensitivity to any component of the tablet.

Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, 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 ischaemic 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 reported 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).

Pregnancy and Lactation

Pregnancy

Sildenafil is not indicated for use in women.

Lactation

Sildenafil is not indicated for use in women.

Geriatrics

Elderly (65 years or over) had a reduced clearance of sildenafil. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered.

Interactions with other medicaments

Effects of other medicinal products on sildenafil

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

Co-administration of sildenafil with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine) resulted in a reduction in sildenafil clearance. Although no increased incidence of adverse events was reported following administration of sildenafil 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, with sildenafil result in increase in sildenafil level . This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics.Co-administration of sildenafil with ritonavir is not advised and in any event the maximum dose of sildenafil should under no circumstances exceed 25mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, with sildenafil result in an increase in sildenafil level . Sildenafil has no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and intraconazole have greater effects.

Administration of a single 100 mg dose of sildenafil with erythromycin, a specific CYP34A inhibitor, result in an increase in sildenafil systemic exposure. There was no effect of azithromycin on the elimination rate constant or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine , a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, can cause an increase in plasma sildenafil concentrations when co-administered together.

Co-administration of sildenafil with endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) result in a decrease of sildenafil level. Concomitant administration of strong CYP3A4 inducers, such as rifampin, cause greater decrease in plasma levels of sildenafil.

Grapefruit juice is a week 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.

No effect on sildenafil pharmacokinetics is seen when tolbutamine, warfarin, phenytoin, selective serotonin reuptake inhibitors, tricyclic antidepressants, thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin coverting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates) are taken together with 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

Sildenafil is a weak inhibitor of the cytochrome P450 . Sildenafil does not 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.

Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil potentiate hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. There is a reduction of supine blood pressure and standing blood pressure when alpha-blocker doxazosin and sildenafil are administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. Some patients may experience symptomic postural hypotension which included dizziness and light-headedness, but not syncope.

There is no interaction when sildenafil is co-administered with tolbutamide or warfarin

Sildenafil not potentiate the increase in bleeding time caused by acetyl salicyclic acid.

Sildenafil not potentiate the hypotensive effects of alcohol with mean maximum blood alcohol levels of 80 mg/dl.

There is reduction on supine systolic blood pressure when sildenafil is taken with amlodipine in hypertensive patients. Sildenafil does not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Side Effects

The most commonly reported adverse reactions among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion. In the table below all medically important adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common, common, uncommon, rare. In addition, the frequency of medicinally important adverse reactions reported from post-marketing experience is included as not known.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA System Organ Class	**Adverse Reaction**
Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	headache
Common	Dizziness
Uncommon	Somnolence, Hypoaesthesia
Rare	Cerebrovascular accident, Syncope
Not known	Transient ischaemic attack, Seizure, Seizure recurrence
Eye disorders	
Common	Visual disorders, Visual color distortion
Uncommon	Conjunctival disorders, Eye disorders,
	Lacrimation disorders, Other eye disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion, Visual field defect.
Ear and labyrinth disorders	
Uncommon	Vertigo, Tinnitus
Rare	Deafness
Vascular disorders	
Common	Flushing
Rare	Hypertension, Hypotension
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Rare	Myocardial infarction, Atrial fibrillation
Unknown	Ventricular arrhythmia, Unstable angina, Sudden cardiac death
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia, Diarrhea
Uncommon	Vomiting, Nausea, Dry mouth
Urinary and renal disorders	
Common	Urinary tract infection
Skin, subcutaneous and soft tissue disorders	
Uncommon	Skin rash
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Reproductive system and breast disorders	
Common	Urinary tract infection
Not known	Priapism, Prolonged erection
General disorders and administration site conditions	
Uncommon	Chest pain, Fatigue

The following events occurred in patients; however causal relationship to sildenafil is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a whole : face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular : AV block, migraine, syncope, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive : glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic : anemia and leucopenia

Metabolic and nutritional : thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal : arthritis, arthrosis, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous : ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, depression, insomnia, abnormal dreams, reflexes decreased.

Respiratory : asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages : urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses : mydriasis, cojuctivitis, photophobia, eye pain, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital : cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

Symptoms and Treatment of Overdose
After administration of single 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 not eliminated in the urine.

Storage
Store below 30°C and protect from moisture.

Shelf life
24 months

Presentation

1. 1x4 tablet packed in PVC/PVDC-Alu blisters along with package insert.

Manufactured by:
HETERO LABS LIMITED
Unit-V, Sy.No. 439, 440, 441 & 458
TSIIC Formulation SEZ, Polepally village, Jadcherla Mandal,
Mahaboobnagar District, Telangana, India

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