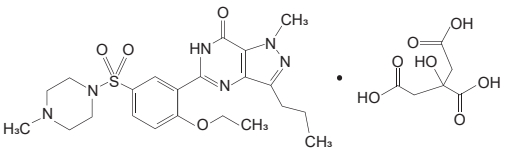
Getfil™

(S i l d e n a f i l)

Film-coated Tablets
25mg, 50mg, & 100mg

گیٹفِل

DESCRIPTION
Getfil (Sildenafil), an oral therapy for erectile dysfunction, is the citrate salt of Sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Chemically, it is 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. Its molecular formula is $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ and the structural formula is:



Sildenafil Citrate

QUALITATIVE & QUANTITATIVE COMPOSITION
Getfil (Sildenafil) is available for oral administration as:

Getfil Tablets 25mg
Each film-coated tablet contains:
Sildenafil Citrate USP equivalent to Sildenafil…25mg

Getfil Tablets 50mg
Each film-coated tablet contains:
Sildenafil Citrate USP equivalent to Sildenafil…50mg

Getfil Tablets 100mg
Each film-coated tablet contains:
Sildenafil Citrate USP equivalent to Sildenafil…100mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.
The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide 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 is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by Sildenafil results in increased corpus cavernosum levels of cGMP. Therefore, sexual stimulation is required in order for Sildenafil to produce its intended beneficial pharmacological effects.

Pharmacokinetics
Absorption
Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 minutes to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of Sildenafil AUC and C_{max} increase in proportion with dose within the recommended dose range (25-100mg).
When Sildenafil is taken with food, 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%.

Distribution
The mean steady state volume of distribution (V_d) for Sildenafil is 105L, indicating distribution into the tissues. After a single oral dose of 100mg, the mean maximum total plasma concentration of Sildenafil is approximately 440ng/mL (CV 40%). Since Sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for Sildenafil of 18ng/mL (38 nM). Protein binding is independent of total drug concentrations.
In healthy volunteers receiving Sildenafil (100mg single dose), less than 0.0002% (average 188ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Metabolism
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of Sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to Sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for Sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4h.

Elimination
The total body clearance of Sildenafil is 41L/h with a resultant terminal phase half-life of 3-5h. 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 administered oral dose).

Special Population
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%.

Patients with Renal Impairment
In subjects with mild to moderate renal impairment (creatinine clearance = 30-80mL/min), the pharmacokinetics of Sildenafil were not altered after receiving a 50mg single oral dose. The mean AUC and C_{max} of the N-desmethyl metabolite increased up to 126% and up to 73% respectively, compared to age-matched volunteers with no renal impairment. In subjects with severe renal impairment (creatinine clearance <30mL/min), Sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased by 200% and 79% respectively.

Patients with Hepatic Impairment
In subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) Sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched subjects with no hepatic impairment. The pharmacokinetics of Sildenafil in patients with severely impaired hepatic function have not been studied.

THERAPEUTIC INDICATIONS
Getfil (Sildenafil) is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
In order for Getfil (Sildenafil) to be effective, sexual stimulation is required.

DOSAGE AND ADMINISTRATION
Adults
The recommended dose of Getfil (Sildenafil) is 50mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100mg or decreased to 25mg. The maximum recommended dose of Getfil (Sildenafil) is 100mg. The maximum recommended dosing frequency is once per day. If Getfil (Sildenafil) is taken with food, the onset of activity may be delayed compared to the fasted state.

Special Population
Elderly
Dose adjustments are not required in elderly patients (≥ 65 years old).

Patients with Renal Impairment
The dosing recommendations described in 'Adults' apply to patients with mild to moderate renal impairment (creatinine clearance = 30-80mL/min).
Since Sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30mL/min) a 25mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50mg up to 100mg as necessary.

Patients with Hepatic Impairment
Since Sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50mg up to 100mg as necessary.

Pediatric Population
Getfil (Sildenafil) is not indicated for individuals below 18 years of age.

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

ADVERSE REACTIONS
Following adverse reactions have been reported with the use of Sildenafil:

Very Common:
Headache.

Common:
Dizziness, visual color distortions, visual disturbance, vision blurred, flushing, hot flush, nasal congestion, nausea and dyspepsia.

Uncommon:
Rhinitis, hypersensitivity, somnolence, hypoesthesia, lacrimation disorders, eye pain, photophobia, photopsia, ocular hyperemia, visual brightness, conjunctivitis, vertigo, tinnitus, tachycardia, palpitations, hypertension, hypotension, epistaxis, sinus congestion, gastro oesophagael reflux disease, vomiting, upper abdominal pain, dry mouth, rash, myalgia, pain in extremity, hematuria, chest pain, fatigue, feeling hot and heart rate increased.

Rare:
Cerebrovascular accident, transient ischemic attack, seizure, seizure recurrence, syncope, Non-arteritic Anterior Ischemic Optic Neuropathy (NAION), retinal vascular occlusion, retinal hemorrhage, 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 hyperemia, eye irritation, abnormal sensation in eye, eyelid oedema, scleral discoloration, deafness, sudden cardiac death, myocardial infarction, ventricular arrhythmia, atrial fibrillation, unstable angina, throat tightness, nasal oedema, nasal dryness, hypoesthesia oral, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), penile hemorrhage, priapism, hematospermia, erection increased and irritability.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

- Sildenafil is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients of the product.
- 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.
- The co-administration of PDE5 inhibitors, including Sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.
- 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 < 90/50mmHg), 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).

PRECAUTIONS

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

Cardiovascular risk factors

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. 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.

Priapism

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).

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.

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

The use of combinations of Sildenafil with other PDE5 Inhibitors, or other Pulmonary Arterial Hypertension (PAH) treatments containing Sildenafil, or other treatments for erectile dysfunction is not recommended.

Effects on vision

Cases of visual defects have been reported spontaneously in connection with the intake of Sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of Sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking Sildenafil and consult a physician immediately.

Hearing Loss

Physicians 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 the intake of PDE5 inhibitors, including Sildenafil.

Counseling Patients About Sexually Transmitted Diseases

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.

Concomitant use with ritonavir

Co-administration of Sildenafil with ritonavir is not advised.

Concomitant use with alpha-blockers

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.

Effect on bleeding

Studies with human platelets indicate that Sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro. Therefore, Sildenafil should be administered to these patients only after careful benefit-risk assessment.

Effects on ability to drive and use machines

Sildenafil has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be considered that dizziness may occur occasionally.

Pregnancy & Nursing Mothers

Sildenafil is not indicated for use by women. There are no adequate and well-controlled studies in pregnant or breast-feeding women.

DRUG INTERACTIONS

- 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 and inducers of these isoenzymes may increase Sildenafil clearance.
- Population pharmacokinetic analysis of clinical study data indicated a reduction in Sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). A starting dose of 25mg should be considered.
- Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500mg twice daily) with Sildenafil (100mg single dose) resulted in a 300% (4-fold) increase in Sildenafil C_{max} and a 1000% (11-fold) increase in Sildenafil plasma AUC. 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, at steady state (1200mg three times a day) with Sildenafil (100mg single dose) resulted in a 140% increase in Sildenafil C_{max} and a 210% increase in Sildenafil AUC. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.
- When a single 100mg dose of Sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500mg twice daily for 5 days), there was a 182% increase in Sildenafil systemic exposure (AUC). Cimetidine (800mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma Sildenafil concentrations when co-administered with Sildenafil (50mg) 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.
- Co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125mg twice a day) with Sildenafil at steady state (80mg three times a day) resulted in 62.6% and 55.4% decrease in Sildenafil AUC and C_{max}, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of Sildenafil.
- Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a serious interaction with Sildenafil.
- 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.
- Riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated.
- Concomitant administration of Sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals.
- Addition of a single dose of Sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril/valsartan alone. Therefore, caution should be exercised when Sildenafil is initiated in patients treated with sacubitril/valsartan.

OVERDOSAGE

In single dose studies of doses up to 800mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200mg 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

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Getfil (Sildenafil) Tablets 25mg are available in blister pack of 4's.
Getfil (Sildenafil) Tablets 50mg are available in blister pack of 4's.
Getfil (Sildenafil) Tablets 100mg are available in blister pack of 4's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

PAK-200021760