# kX Tablet

## Sildenafil Citrate INN

**COMPOSITION:**

**kX-50 Tablet :** Each film coated tablet contains Sildenafil Citrate INN eqvt. to Sildenafil 50 mg.

**kX-100 Tablet :** Each film coated tablet contains Sildenafil Citrate INN eqvt. to Sildenafil 100 mg.

**DESCRIPTION:**

Sildenafil is an inhibitor of phosphodiesterase type 5 (PDE5). The sexual stimulation causes the natural production of nitric oxide which release required quantity of cGMP. PDE5 is present in the corpus cavernosum smooth muscle, vascular & visceral smooth muscle, kidney, lungs & pancreas. Sildenafil has no effect on penile blood flow in the absence of sexual stimulation.

**PHARMACOLOGY:**

Sildenafil is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent Sildenafil. Both Sildenafil and the metabolite have terminal half lives of about 4 hours. 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.

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 cavemosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by Sildenafil causes increased levels of cGMP in the corpus cavemosum, 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.

**INDICATION:**

Sildenafil is used for the treatment of men with erectile dysfunction and pulmonary arterial hypertension (PAH).

**DOSAGE AND ADMINISTRATION:**

**Erectile Dysfunction**

The recommended dose for most patients is 50 mg taken, as needed, approximately 30 - 40 minutes before intercourse. However, Sildenafil may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. It should not be used more than once daily.

The following factors are associated with increased plasma levels of Sildenafil: age >65, hepatic impairment, severe renal impairment, and concomitant use of potent cytochrome P450 3A4 inhibitors (ketoconazole, itraconazole, erythromycin, saquinavir). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients. When Sildenafil is co-administered with a-blocker, patients should be stable on a-blocker therapy prior to initiating Sildenafil treatment and Sildenafil should be initiated at the lowest dose.

**Pulmonary arterial hypertension**

The recommended dose of Sildenafil Citrate is 20 mg three times a day and should be taken approximately 4-6 hours apart, with or without food.

**SIDE-EFFECTS:**

Like all medicines, Sildenafil can cause side-effects although not everybody gets them. The side-effects reported in association with the use of Sildenafil are usually mild to moderate and of a short duration.

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

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

**Nervous:** ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, hypesthesia.

**Respiratory:** asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis.

**Cardiovascular:** angina pectoris, AV block migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram and cardiomyopathy.

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

**Hemic and Lymphatic:** anemia and leukopenia.

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

**Skin and Appendages:** urticaria, pruritus, sweating, skin ulcer, exfoliative dermatitis.

**Special Senses:** sudden decrease or loss of hearing, mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, ear pain, eye hemorrhage, cataract, dry eyes.

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

**CONTRAINDICATIONS:**

Sildenafil has 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. Sildenafil is also contraindicated in patients with a hypersensivity to any component of the tablet.

**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 Slidenafil, it is important to note the following:** Caution is advised when Phosphodiesterase Type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including Sildenafil, and a-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 symptomatic hypotension (e.g. dizziness, fainting lightheadedness).

**Regard should be given:**

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

Sildenafil has systemic vasodilatory properties and may augment the blood pressure lowering effect of other anti-hypertensive medications.

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

**WARNINGS:**

There is a cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction with Sildenafil should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. Sildenafil has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (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 consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory 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 subaortic stenosis) and those with severely impaired autonomic control of blood pressure.

There is no controlled clinical data on the safety or efficacy of Sildenafil 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);
- Patients with sickle cell or related anemias.

**DRUG INTERACTTONS:**

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes 15 may reduce Sildenafil clearance and inducers of these isoenzymes may increase Sildenafil clearance. Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma Sildenafil concentrations when coadministered with Sildenafil (50 mg). When a single 100 mg dose of Sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in Sildenafil systemic exposure (AUC). Co-administration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with Sildenafil (100 mg single dose) resulted in a 140% increase in Sildenafil Cmax and a 210% increase in Sildenafil AUC. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in Sildenafil clearance when it was coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine). In another study co-administration with the HIV protease inhibitor ritonavir, a highly potent P450 inhibitor, at steady state (500 mg bid) with Sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in Sildenafil Cmax and a 1000% (11-fold) increase in Sildenafil plasma AUC. At 24 hours, the plasma levels of Sildenafil were approximately 200 ng/ml, compared to approximately 5 ng/ml when Sildenafil was dosed alone. Although the interaction between other protease inhibitors and Sildenafil has not been studied, their concomitant use is expected to increase Sildenafil levels. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma levels of Sildenafil. The AUC of the active metabolite, N-desmethyl Sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by 16 nonspecific betablockers. These effects on the metabolite are not expected to be of clinical consequence.

**PREGNANCY & LACTATION**:

Sildenafil is not indicated for use in women.

**Geriatric Use:** Healthy elderly volunteers (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.

**OVERDOSAGE**:

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

**STORAGE**:

Store in a cool and dry place, away from light. Keep out of reach of children.

**COMMERCIAL SUPPLY**:

**kX-50 Tablet:** Each box contains 1 blister strip of 5 film-coated tablets.

**kX-100 Tablet:** Each box contains 1 blister strip of 5 film-coated tablets.

**Manufactured by :**

**KEMIKO PHARMACEUTICALS LTD.**

Bangladesh