SILDENAFIL CITRATE
KADAGRA
100mg Film-Coated Tablet

Selective Phosphodiesterase-5 (PDE5) Inhibitor

**Formulation:**
Each Tablet contains:
Sildenafil (as Citrate) ............ 50 mg
Sildenafil (as Citrate) ............ 100 mg

**DESCRIPTION:**
Sildenafil Citrate is an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP) - phosphodiesterase type 5 (PDE5).

Sildenafil Citrate is designated chemically as 1-[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1Hpyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl] sulfonil]-4-Methylpiperazine citrate and has the following structural formula: Sildenafil Citrate is a white to off-white crystalline powder with a solubility of 3.5g/ml in water and a molecular weight of 666.7. Sildenafil Citrate is formulated as blue, film-coated diamond-shaped tablets 50 mg and 100 mg of sildenafil for oral administration, in addition to the active ingredient, Sildenafil Citrate, each tablet contains the following inactive ingredients: maize starch, lactose, microcrystalline cellulose, povidone, croscarmellose sodium, sodium, citric acid, and magnesium stearate, sodium starch glucronate, croscarmellose sodium, talcum, dicalcium phosphate.

**PHARMACOKINETICS:**
Sildenafil is rapidly absorbed after a dose by mouth, with a bioavailability of about 40%. Peak plasma concentrations are attained within a 30 to 120 minutes. The rate of absorption is reduced when sildenafil is given with food. Sildenafil is widely distributed into tissues and is about 96% bound to plasma proteins. It is metabolized in the liver mainly by cytochrome P450 isoenzymes CYP3A4. (the major route) and CYP2C9. The major metabolite, N-desmethylsildenafil (UK-103320) also has some activity. The terminal half-lives of sildenafil and the N-desmethyl metabolite are about 4 hours. Sildenafil is excreted as metabolites, mainly in the faeces, and to a lesser extent the urine. Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

**MECHANISM OF ACTION:**
The physiologic mechanism 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 NO by inhibiting 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.

**INDICATION:**
Sildenafil Citrate (Filagra) is indicated for the treatment of Erectile Dysfunction.

**DOSE AND ADMINISTRATION:**
Sildenafil is a phosphodiesterase type 5 inhibitor used in the treatment and management of erectile dysfunction and pulmonary arterial hypertension. It is given by mouth as the citrate although doses are expressed in terms of the base; 14 mg of Sildenafil Citrate is equivalent to about 10 mg of sildenafil.

In erectile dysfunction the usual dose is equivalent to sildenafil 50 mg taken about one hour before sexual intercourse. The dose may be increased or decreased depending on the response. The maximum recommended dose is 100mg, and Sildenafil should not be taken more than once in 24 hours. An initial dose of 25 mg has been suggested in the USA for patients over 65 years of age, though no more than 25 mg daily is advised in patients taking sildenafil with inhibitors of cytochrome P450 isoenzyme CYP3A4: licensed drug information states that the dose should not exceed 25 mg every 48 hours if given with ritonavir, although such a combination is best avoided entirely. In patients stabilized on alpha blocker therapy, an initial dose of sildenafil 25 mg should be considered. Higher doses should not be taken with 24 hours of an alpha blocker because of the risk of symptomatic hypotension.

For doses in hepatic and renal impairment: To improve exercise ability in pulmonary arterial hypertension, sildenafil is given orally in a dose of 20 mg three times daily. The dose may need adjustment to account for drug interactions (see above) although licensed drug information suggests that in these patients no adjustment is required when given alone, but when given with erythromycin or saquinavir. It also suggests that no adjustment is generally needed for pulmonary hypertension patients with renal or hepatic impairment, although patients with severe hepatic impairment (Child-Pugh category C) have not been studied. Although not licensed in the UK the BNFC includes a dose for children aged from neonates up to 18 years of age, of 250 to 500 micrograms/kg given orally every 4 to 8 hours, adjusted according to response up to a maximum of 2 mg/kg every 4 hours. Treatment should be withdrawn gradually in neonates.

**ADMINISTRATION IN HEPATIC IMPAIRMENT:**
In the management of erectile dysfunction, an initial dose of 25 mg of sildenafil is recommended by licensed drug information in patients with hepatic impairment.

**ADMINISTRATION IN RENAL IMPAIRMENT:**
In the management of erectile dysfunction, an initial dose of 25 mg of sildenafil is recommended by licensed drug information in patients with severe renal impairment (creatinine clearance less than 30ml/minute).

**ERECTILE DYSFUNCTION:**
Sildenafil, an inhibitor or phosphodiesterase type-5, is used as an oral therapy for erectile dysfunction. It is effective in erectile dysfunction of psychogenic causes and organic causes such as diabetes mellitus, spinal-cord injury and prostatectomy.

**PRECAUTIONS:**
Caution is required in patients with hepatic or severe renal impairment, and dosage recution of Filagra may be necessary. Care is also needed in patients with anatomical deformation of the penis or hematological disorders that may predispose them to priapism. In the event of prolonged erection (for more than 4 hours), patients should seek medical assistance, as penile tissue damage and permanent loss of potency can occur. Patients are also advised to stop taking Filagra and seek medical advice in cases of sudden visual or hearing loss.

**NITRATES:**
Giving sildenafil 50 mg to patients receiving isosorbide mononitrate, or sublingual glyceryl trinitrate given 1 hour after sildenafil, resulted in substantially greater decreases in blood pressure that when the nitrate was given alone in 2 crossover studies in patines with angina. Treatment-related adverse effects were reported in 8 of 16 patients who took sildenafil with isosorbide monoamine and 3 of 15 who received sildenafil with glyceryl trinitrate. Sildenafil should not be taken with nitrates.

**INTERACTIONS:**
Sildenafil or other phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. Sildenafil may also enhance the hypotensive effect of nicorandil and use of the two drugs together should be avoided. Symptomatic hypotension may also occur when phosphodiesterase type-5 Inhibitors are given with alpha blockers. Generally, the patient should be stabilized on alpha blocker therapy before the phosphodiesterase type-5 inhibitor is started at a low dose and adjusted according to response; minimum dosage intervals have also been recommended in some cases. Drugs that inhibit the cytochrome P450 isoenzyme CYP3A4, such as cimetidine, delavirdine, erythromycin, itraconazole, and HIV-protease inhibitors, may reduce the clearance of phosphodiesterase type-5 inhibitors, necessitating a reduction in dosage. Furthermore, plasma concentrations of phosphodiesterase type-5 inhibitors are significantly increased by ritonavir, requiring even greater dosage reduction, and such combinations should not be given unless absolutely essential. Grapefruit juice should be avoided with sildenafil or other phosphodiesterase type-5 inhibitors as it may increase their plasma concentrations. Inducers of CYP3A4, such as rifampicin, are likely to decrease plasma concentrations of phosphodiesterase type-5 inhibitors.

**ANTIVIRALS:**
Rises in sildenafil concentrations after use of saquinavir or ritonavir were consistent in inhibition of metabolism mediated by the cytochrome P450 isoenzyme CYP3A4. The larger increases seen with ritonavir may be due to its additional inhibition of...
the isoenzyme CYP2C9. Fatal myocardial infarction has been reported in a 47-year-old patient who took sildenafil 25 mg with ritonavir and saquinavir. In a study of 6 HIV-positive men being treated with triple antiretroviral therapy that included indinavir, plasma concentrations of sildenafil were found to be significantly increased compared with historical controls.

**CARDIOVASCULAR RISKS:**
The effects of phosphodiesterase type-5 inhibitors on the cardiovascular system and the potential risks of sexual activity in men with cardiovascular diseases, have been reviewed. There has been considerable uncertainty about the potential cardiovascular risk associated with Filagra treatment. Minor effects associated with vasodilators, such as headache and flushing are relatively common, but in patients without pre-existing cardiovascular risk factors he risk of serious cardiovascular events associated with the drug appears to be low. However there have been reports of myocardial infarction who had no apparent risk factors and a consensus document pointed out that patients with erection dysfunction are mostly 45 years of age and are more likely to have risk factors predisposing them to cardiovascular disease.

**DIHYDROCODEINE:**
The use of dihydrocodeine with sildenafil was associated with priapism in 2 men who had previously been treated successfully with sildenafil. The first patient had two prolonged erections, lasting 4 and 5 hours, and the effect did not recur when the dihydrocodeine was stopped. The second patient had priapism on 3 occasions in the first week of dihydrocodeine treatment, but not in the subsequent 2 weeks despite continuing both drugs.

**IMMUNOSUPPRESSANTS:**
Studies in men with erectile dysfunction who were receiving tacrolimus after kidney transplantation found that sildenafil had no effect on tacrolimus pharmacokinetics. However, the pharmacokinetics profile of sildenafil differed from that reported in healthy subjects: the maximal plasma concentration was higher, the area under the concentration-time curve was increased, and the elimination half-life was prolonged. Reductions in blood pressure were also found when sildenafil was given, although this may have been due to an interaction with verapamil. The authors suggested that an initial dose of 25 mg sildenafil should be used, and that on the days of sildenafil use the doses of antihypertensive drugs may need to be adjusted to blood pressure response.

**ADVERSE EFFECTS:**
Adverse Effects most commonly reported with Filagra are headache, flushing, and dyspepsia. Also common are visual disturbances such as blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, pain and redness of the eyes. Retinal hemorrhage has occurred, and non-arteritic anterior ischaemic optic neuropathy causing permanent loss of vision has been reported rarely. Other common adverse effects include dizziness, insomnia, anxiety, vertigo, epistaxis, nasal decongestion, pyreisa, and gastrointestinal disturbances such as diarrhea and vomiting. Priapism can occur.

Other adverse effects include skin rashes, erythema, alopecia, limb and or back pain, myalgia, facial edema, fluid retention, paresthesia, and urinary tract infection. Dyspnea, cough, rhinitis, sinusitis, bronchitis, and cellulitis can occur. Other reported effects include anemia, leucopenia, gynecomastia, urinary frequency or incontinence, hematuria, and seizures.

Cardiovascular hemorrhage and transient ischaemic attacks have occurred. There have also been reports of palpitation, syncope, hypertension, hypotension, and serious cardiovascular events including myocardial infarction, arrhythmias, tachycardia, unstable angina, and sudden cardiac death.

**CAUTION:**
FOODS, DRUGS, DEVICES AND COSMETICS ACT prohibits dispensing without prescription.

**STORAGE CONDITION:**
Store at temperatures not exceeding 30°C.

**AVAILABILITY:**
Sildenafil Citrate 100 mg Alu-Clear PVC Blister Box of 4 Tablets

Manufactured by: SRI PHARMACARE 27A Mangalam Society, Ring Road Ghodastar Ahmedabad, Mumbai India

Imported and Distributed by: SAHAR INTERNATIONAL TRADING, INC. #354 Aguirre Ave., Phase III BF Homes, Paranaque City, Philippines