Veagra

Sildenafil INN

Presentation
Veagra 50 mg Tablet: Each film coated tablet contains Sildenafil Citrate INN 70.24 mg equivalent to Sildenafil 50 mg.
Veagra 100 mg Tablet: Each film coated tablet contains Sildenafil Citrate INN 140.48 mg equivalent to Sildenafil 100 mg.

Description
Sildenafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE 5 by Sildenafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Sildenafil has no effect in the absence of sexual stimulation.

Clinical Pharmacology
Mechanism of action: The physiological 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 covernosum, but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE 5), 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 effects in the absence of sexual stimulation. ***Pharmacokinetics and Metabolism:*** Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (range 25-63%). 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. 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 high fat meal, the rate of absorption is reduced. ***Metabolism and Excretion:*** Sildenafil is cleared by hepatic microsomal isoenzymes. 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. *Geriatrics:* Healthy elderly volunteers (65 years or over) had a reduced clearance of Sildenafil, resulting in approximately 84% and 107% higher plasma AUC values of sildenafil compared to those seen in healthy younger volunteers. ***Indication and Usage:*** Sildenafil is indicated for the treatment of erectile dysfunction and pulmonary arterial hypertension.

Dosage and Administration
Erectile dysfunction: For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day. 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. Sildenafil was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated. When Sildenafil is co-administered with an alpha-blocker, patients should be stable on alphablocker 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. ***Adverse Effects:*** Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury. ***Cardiovascular:*** angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy. ***Digestive:*** Vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function test abnormal, rectal hemorrhage, gingivitis. ***Hemic and Lymphatic:*** anemia and Leukopenia. ***Metabolic and Nutritional:*** thirst, edema, gout, unstable diabetes, hyper glycemia, peripheral edema, hyper uricemia, hypoglycemic reaction, hypernatremia. ***Musculoskeletal:*** arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis. ***Nervous:*** ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia. ***Respiratory:*** asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased. ***Skin and Appendages:*** urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exofoliative 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, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

Contraindications
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. Sildenafil is contraindicated in patients with a known hypersensitivity 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 Sildenafil, it is important to note the followint: Caution is advised when Phosphodiesterase Type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including Sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodllators 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, 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, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor. ** Safety of combined use of PDE5 inbibitors and alpha-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. Patients on multiple antihypertensive medications were included in the pivotal clinical trials for Sildenafil. In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and Sildenafil, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted. The safety of Sildenafil is unknown in patients with bleeding sisorders and patients with active peptic ulceration. Sildenafil should be used with caution in patients witn 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 combinatons is not recommended.

Warnings
There is a 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 underiying 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. 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. If Sildenafil is prescribed to patients taking rltonavir, caution should be used. Data from subjects 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 in some healthy volunteers exposed to 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.

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 15 may reduce Sildenafil clearance and inducers of these isoenzymes may increase Sildenafil clearance. Cimetidine (800 mg), a nonspecific CYPinhibitor, caused a 56% increase in plasma Sildenafil concentrations when coadministred with Sildenafil (50 mg) to healthy volunteers. When a singla 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), In addition, in a study performed in healthy male volunteers, 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% increases in Sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. 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 in healthy male volunteers, coadministration with the HIV protease inhibitor ritonavir, which is 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 still approximately 200 ng/mL, compared to approximately 5 ng/mL when Sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Although the interaction between other protease inhibitors and Sildenafil has not been studied, their concomitant use is expected to increase Sildenafil levels. In a study of healthy male volunteers, co-administration of Sildenafil at steady atate (80 mg t.i.d) with endothelin receptor antagonist bosentan(a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d) resulted in a 63% decrease of Sildenafil AUC and a 55% decrease in Sildenafil Cmax. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma level of Sildenafil. Single doses of antacid(magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of Sildenafil. Pharmacokinetic data from patients in clinical trials showed no effect on Sildenafil pharmacokinetice of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressant), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl Sildenafil, was increased 62% by loop and potassium-sparing diuretics and102% by 16 nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Pregnancy, Nursing Mothers and Pediatric Use
Pregnancy Category B. Sildenafil is not indicated for use in newborns, children, or women. ***Geriatric Use:*** Healthy elderly volunteers (65 years or over) had a reduced clearance of Sildenadil 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 dose but incidence rates and severities were incerased. 24 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,

How Supplied:
Veagra 50 mg Tablet: Each box contains 1 X 4's tablets alu PVC blister strip.
Veagra 100 mg Tablet: Each box contains 1 X 4's tablets alu PVC blister strip.

Manufactured by:
Astra Biopharmaceuticals Ltd.
Gouripur, Ashulia, Dhaka, Bangladesh