Rx

3018911

SILDENAFIL CITRATE CHEWABLE TABLETS

KAMAGRA CHEWABLE TABLETS

COMPOSITION

Each pack contains :
Sildenafil Citrate Chewable tablets 50mg / 100mg
Each uncoated Chewable tablets contains :
Sildenafil Citrate IP
equivalent to Sildenafil 50mg / 100mg
Colour : Lake of Sunset Yellow FCF, Lake of Quinoline Yellow, Erythrosine and Sunset Yellow FCF & Quinoline Yellow WS

Pharmacological Properties
Pharmacodynamic properties

(Sildenafil citrate) is the citrate salt of Sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specfic phosphodiesterase type 5(PDE5).
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 enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. Sildenafil has no direct relaxant effect on isolated human 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.

Pharmacokinetic properties

Absorption
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. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil, AUC and Cmax increase in proportion with dose over the recommended dose range (25-100mg).
When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in Tmax of 60 minutes and a mean reduction in Cmax of 29%.

Distribution
The mean steady state volume of distribution (Vd) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.
In healthy volunteers receiving Sildenafil Citrate (100 mg single dose), less than 0.0002% (average 188 ng) 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 metabolized, with a terminal half-life of approximately 4 hours.

Elimination
The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

infrequently with Sildenafil citrate. 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.
Agents for the treatment of erectile dysfunction 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 anaemia, multiple myeloma or leukaemia).
Agents for the treatment of erectile dysfunction should not be used in men for whom sexual activity is inadvisable.
The safety & efficacy of combinations of Sildenafil Citrate with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.
Controlled studies of drug interactions between Sildenafil Citrate and other antihypertensive medications have not been performed.
Sildenafil Citrate has no effect on bleeding time, including during co-administration with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of Sildenafil Citrate to patients with bleeding disorders or active peptic ulceration. Therefore Sildenafil Citrate should be administered with caution to these patients.

DRUG INTERACTIONS

Effects of other drugs on Sildenafil
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.
In vivo studies:
Cimetidine, a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with Sildenafil to healthy volunteers.
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CTP3A4 inhibitors (such as itraconazole, ketoconazole, erythromycin, and cimetidine). However there was no increased incidence of adverse events in these patients.
Single doses of antacid (magnesium hydroxide / aluminium hydroxide) did not affect the bioavailability of Slidenafil.
Population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, ACE inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

Effects of Sildenafil on other medicines
In vitro studies:
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50>150 microM). Given sildenafil peak plasma concentrations of approximately 1 microM after recommended doses, it is unlikely that it will alter the clearance of substrates of these isoenzymes.
In vivo studies:
No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.
Sildenafil did not potentiate the increase in bleeding time caused by aspirin (150 mg).
Sildenafil did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dL.
No interaction was seen when Sildenafil was co-administered with amlodipine in hypertensive patients. The mean additive reduction on supine blood pressure (systolic, 8 mmHg; diastolic, 7 mmHg) was of a similar magnitude to that seen when Sildenafil was administered alone to healthy volunteers.
Analysis of the safety database showed no difference in the side effect profile in patients taking Sildenafil with and without anti-hypertensive medication.
Sildenafil was shown to potentiate the hypotensive effect of

acute and chronic nitrates. Therefore, use of nitrates or nitric oxide donors with Sildenafil is contraindicated (see Contraindications).

Pregnancy and lactation

KAMAGRA CHEWABLE TABLETS are not indicated for use by women.
No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to **KAMAGRA CHEWABLE TABLETS** before driving or operating machinery.

ADVERSE EFFECTS

Sildenafil is generally well tolerated. Adverse reactions were mild to moderate in nature and the incidence and severity increased with dose. Commonly reported adverse events to Sildenafil include the following : headache (16%), dyspepsia (7%), nasal congestion (4%) and skin rash (2%). The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance and blurred vision.
Hypersensitivity, somnolence, hypoaesthesia, eye pain, photophobia, vertigo, tinnitus, tachycardia, palpitations, chest pain, vomiting, abdominal pain, dry mouth, rash, myalgia, fatigue, have rarely been reported with sildenafil.

OVERDOSE
In single dose volunteer 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, 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.

DOSAGE AND METHOD OF ADMINISTRATION
For oral use.

<u>Use in adults</u>
For most patients, the recommended dose is 50 mg taken, as needed. Based on effectiveness and tolerance, 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 level of Sildenafil : age > 65 (40% increase in AUC), hepatic impairment (e.g. cirrhosis, 80%) severe renal impairment (creatinine clearance <30mL / min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitor [Ketoconazole, Itraconazole, Erythromycin (182%), Saquinavir (210%)]. 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.

PRESENTATION
Available in a Blister combipack of 4 Tablets.
(Orange, Pineapple, Strawberry, Banana)

Store below 30°C.

KEEP OUT OF THE REACH OF CHILDREN.

Manufactured in India by :
ajanta pharma limited
Ajanta House, Charkop,
Kandivli (W), Mumbai 400 067.

Pharmacokinetics in special patient groups

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%.

Renal insufficiency
In volunteers with mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 L/min) renal impairment, the pharmacokinetics of a single oral dose of Sildenafil Citrate (50 mg) were not altered. In volunteers with severe (CLcr<30mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and Cmax (88%) compared to age-matched volunteers with no renal impairment.

Hepatic insufficiency
In volunteers with hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment.

Indications
KAMAGRA CHEWABLE TABLET is indicated for the treatment of erectile dysfunction.

Contraindications

Use of KAMAGRA CHEWABLE TABLET is 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 co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated. Doctors should discuss with patients the contra-indication of KAMAGRA CHEWABLE TABLET with concurrent organic nitrates.
In the following patients: age>65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitor (e.g., erythromycin); plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safety co-administered at this time point.

Warnings and precautions for use

There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including Sildenafil Citrate, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.
A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes and identify appropriate treatment.
Sildenafil Citrate has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers. 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.
There is no controlled clinical data on the safety or efficiency of Sildenafil citrate 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