Sildenafil and Dapoxetine Tablets

Super KAMAGRA*

COMPOSITION : Each film coated tablet contains :

Sildenafil Citrate equivalent to Sildenafil	100 mg
Dapoxetine Hydrochloride equivalent to Dapoxetine	60 mg

DESCRIPTION

Sildenafil : A selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Dapoxetine : A short acting serotonin reuptake inhibitor (SSRI) developed specifically for the treatment of premature ejaculation.

CLINICAL PHARMACOLOGY

Mechanism of Action : ***Sildenafil :*** 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 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.

Dapoxetine : Dapoxetine exhibits its efficacy by primarily inhibiting the reuptake of the serotonin transporter. It was also shown to bind and inhibit the reuptake transporters of dopamine and norepinephrine.

Pharmacokinetics

Sildenafil : *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 a high fat meal, 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%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

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). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach

Dapoxetine : Dapoxetine is rapidly absorbed after oral administration with a peak plasma concentration (T_{max}) occurring between 1.4 and 2.0 hours. This is followed by a rapid decline in plasma concentration, to about 5% of peak concentration at 24 hours. Both the area under the curve (AUC) and C_{max} increased proportionately with doses up to 100 mg. The mean initial half-life of dapoxetine after a single dose is 0.5 to 0.8 hours and this decreased slightly to 0.4 to 0.6 hours after multiple doses for 6 days. The terminal half-life of dapoxetine was 15 to 19 hours after a single dose and 20 to 24 after multiple doses.

Dapoxetine undergoes hepatic metabolism to 2 metabolites, desmethyldapoxetine and didesmethyldapoxetine, both of which have much lower plasma concentrations compared with dapoxetine. Information on specific isoenzymes involved in metabolism and volume of distribution and details on excretion had not been published at press time.

INDICATIONS : For the treatment of male erectile dysfunction and premature ejaculation.

CONTRAINDICATIONS

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 administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated. Sildenafil is not indicated for use in women and individuals below 18 years of age.

WARNINGS & PRECAUTIONS

Drug Interactions : *Sildenafil : Effects of other drugs on sildenafil*

In vitro studies: 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 (800 mg), a non-specific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

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 co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine). It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Ritonavir, a highly potent P450 inhibitor, resulted in 300% increase in sildenafil C max and 1000% increase in sildenafil plasma AUC. Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), 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 and 102% by non-specific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Effects of sildenafil on other drugs : *In vitro studies*: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC 50 > 150 mM). Given sildenafil peak plasma concentrations of approximately 1μM after recommended doses, it is unlikely that sildenafil 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 (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

No interaction was seen when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additional 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.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

General : 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).

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment. There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

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).

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.

Sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, Sildenafil should be administered with caution to these patients. Simultaneous administration of sidenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in some patients. Therefore, sidenafil doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker.

A minority of patients with the inherited condition, retinitis pigmentosa, have genetic disorders of retinal phosphodiesterases. There is no safety information on the administration of sildenafil to patients with retinitis pigmentosa. Therefore, sildenafil should be administered with caution to these patients.

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.

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.

Dapoxetine : Currently, there are no documented drug-drug interactions associated with dapoxetine. Coadministration of dapoxetine with ethanol did not produce any significant pharmacokinetic changes.

Pregnancy : There are no adequate and well-controlled studies of combination of Sildenafil and Dapoxetine in pregnant women. It is not indicated in women.

Lactation : Combination of Sildenafil and Dapoxetine is not indicated in nursing mothers.

Paediatric Use : Combination of Sildenafil and Dapoxetine is not indicated in children.

ADVERSE REACTIONS

Sildenafil : The most frequent side effects reported with sildenafil use include headache, flushing, dyspepsia, nasal congestion, abnormal vision (mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision), urinary tract infection, diarrhea, dizziness, and rash. Serious cardiovascular, cerebrovascular and vascular events have been reported in temporal association with sildenafil use. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

Dapoxetine : The most common adverse events associated with dapoxetine were nausea, diarrhea, dizziness, and headache.

DOSAGE :

The recommended dose is once daily approximately 1 hour before sexual activity.

STORAGE : Store at a temperature below 30°C., Protect from light & moisture.
KEEP OUT OF THE REACH OF CHILDREN

PRESENTATION : Available in blister of 4 tablets.

A product of:

ajanta pharma limited

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