Sildenafil Citrate Effervescent Tablets 100 mg

KAMAGRA EFFERVESCENT TABLETS 100 MG (Orange Flavour)

COMPOSITION
Each effervescent tablet contains :
Sildenafil citrate equivalent to Sildenafil 100 mg

PHARMACOLOGICAL ACTION
KAMAGRA restores impaired erectile function by increasing blood flow to the penis, in response to sexual stimulation.
Sildenafil is a selective inhibitor of cGMP specific 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 but enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, during sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum allowing the inflow of blood.

Absorption
KAMAGRA 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%). The oral pharmacokinetics of KAMAGRA is proportional over the recommended dose range (25-100 mg).
When KAMAGRA is taken with a high fat meal, 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 (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.
In healthy volunteers receiving KAMAGRA (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 PDE 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 metabolised, 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).

Pharmacokinetics in Special Patient Groups:
Elderly
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal Insufficiency
In volunteers with mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of KAMAGRA (50 mg) were not altered. In volunteers with severe (CLcr <30 mL/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.

Preclinical Safety Data
KAMAGRA shows no evidence of any mutagenic or carcinogenic potential.

INDICATIONS
KAMAGRA is indicated only for the treatment of erectile dysfunction.

CONTRA-INDICATIONS
Use of KAMAGRA 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 (see Pharmacological Action), KAMAGRA 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 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 inhibitors (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 safelyco-administered at this time point.

WARNINGS
There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including KAMAGRA, 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.
KAMAGRA 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 efficacy of KAMAGRA 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 infrequently since market approval of KAMAGRA. 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 and efficacy of combinations of KAMAGRA 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 KAMAGRA and other antihypertensive medications have not been performed.
KAMAGRA 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 KAMAGRA to patients with bleeding disorders or active peptic ulceration. Therefore KAMAGRA should be administered with caution to these patients.

INFORMATION FOR PATIENTS
The use of KAMAGRA offers no protection against sexually transmitted diseases. Counseling of patients about protective measures necessary to guard against sexually transmitted diseases, including the human immunodeficiency virus (hiv/aids) should be considered.
Precautions against unwanted pregnancy should be taken.
Physicians should discuss with patients the contraindication of KAMAGRA with regular and/or intermittent use of organic nitrates.
Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors.
Patients who experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.
Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of KAMAGRA. 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 may result.

Pregnancy and Lactation
KAMAGRA is not indicated for use in women.
No teratogenic effects, impairment of fertility or adverse effects on peri/postnatal development were found in reproduction studies in rats and rabbits following oral administration of sildenafil.
There was no effect on sperm motility or morphology after single 100 mg oral doses of KAMAGRA in healthy volunteers.

Effects on Ability to Drive and Use Machines
As dizziness and altered vision were reported in clinical trials with KAMAGRA, patients should be aware how they react to KAMAGRA and exercise caution before driving, operating hazardous machinery or performing hazardous tasks.

DOSAGE AND DIRECTIONS FOR USE
KAMAGRA tablets are for oral administration.
Use in Adults
The recommended dose is 50 mg, taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day.

Function
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil. Therefore the following factors are associated with increased plasma levels of sildenafil:
Age >65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance <30 mL/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin, ketoconazole, itraconazole, 200%).
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.
KAMAGRA 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.

Use in Children
KAMAGRA is not indicated for use in children.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in temporal association with the use of KAMAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of KAMAGRA without sexual activity. Others were reported to have occurred hours to days after the use of KAMAGRA and sexual activity. It is not possible to determine whether these events are related directly to KAMAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for further important cardiovascular information).
Headache, flushing, dizziness, hypotension, angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy have also been reported.
Ocular: abnormal vision (Mild and transient. Predominantly colour tinge to vision, but also increased perception of light or blurred vision). Diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema. Conjuctivitis, photophobia, eye haemorrhage, cataract, dry eyes and eye pain
Urogenital: cases of priapism (prolonged erection) have been reported. Cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema, anorgasmia and haematuria have also been reported.
Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.
Digestive: dyspepsia, 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, and hypernatremia.
Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, and tenosynovitis, bone pain, myasthenia, synovitis.
Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, and hypesthesia.
Respiratory: nasal congestion, asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.
Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.
Special Senses: tinnitus, deafness, ear pain
At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.
Interactions with Other Medicaments and other forms of interaction:

Effects of other drugs on KAMAGRA
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 CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with KAMAGRA (50 mg) to healthy volunteers.
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 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 KAMAGRA.
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 KAMAGRA 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 KAMAGRA 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 metabolised by CYP2C9.
KAMAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).
KAMAGRA (50 mg) 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 KAMAGRA (100 mg) 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 KAMAGRA was administered alone to healthy volunteers (see Pharmacodynamic properties).
Analysis of the safety database showed no difference in the side effect profile in patients taking KAMAGRA with and without anti-hypertensive medication.
KAMAGRA was shown to potentiate the hypotensive effect of acute and chronic nitrates. Therefore, use of nitrates or nitric oxide donors with KAMAGRA is contraindicated (see Contraindications).
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
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 were 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.

PRESENTATION
Available in a strip pack of 1's tablet.

STORAGE
Store at a temperature below 30°C.
Protect from light & moisture.

KEEP OUT OF THE REACH OF CHILDREN.

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