FRONT

KAMAGRA TABLETS

Rx
Sildenafil Citrate Tablets

FOURTH FOLD

COMPOSITION:
Each film coated tablet contains:
Sildenafil citrate
equivalent to Sildenafil....50/100 mg

THERAPEUTICAL CODE:
G04BE03

DOSAGE FORM
Film Coated Tablets

THIRD FOLD

PRODUCT DESCRIPTION
Green coloured diamond shaped film coated tablet engraved with 'ap' logo on one side and 'KGR 50 / KGR 100' on the other side.

MECHANISM OF ACTION:
Kamagra i.e. sildenafil citrate is a new potential oral therapy for the treatment of erectile dysfunction. It is a selective inhibitor of phosphodiesterase-5 and classified as a vasodilator-peripheral.
PDE-5 is an enzyme found mainly in the corpus cavernosum. Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase-5 i.e. PDE5.The physiologic mechanism of

FOURTH FOLD

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. Thus sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increase level of cGMP in the corpus cavernosum resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended dose has no effect in the absence of sexual stimulation.

SECOND FOLD

PHARMACOKINETICS:
Absorption: Sildenafil tablet undergoes rapid absorption after rapid oral administration. 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 Tmax of 60 minutes and a mean reduction in Cmax of 29%.
Distribution: The mean state volume of distribution (Vss) for sildenafil is 105L, 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.

FOURTH FOLD

Metabolism: It is cleared predominantly by the CYP 3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. It is converted into an active metabolite by N-desmethylation. This metabolite has a PDE selectivity profile similar and in vitro potency for PDE5~50% parent drug. Plasma concentrations of metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl is further metabolised, with terminal half-life of approximately 4 hours.
Elimination: Sildenafil is excreted as metabolites predominantly in the feces (~80%) and to a lesser extent in the urine (~13%). The total body clearance of Sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours.

THIRD FOLD

Pharmacokinetics in Special Population:
Elderly: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations of approximately 40% greater than those seen in healthy younger volunteers (18-45 years).
Renal Insufficiency: In volunteers with mild (CLcr = 50-80mL/min) and moderate (CLcr = 30-49mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50mg) were not altered. In volunteer with severe (Clcr 30ml/min) renal impairment, sildenafil clearance was reduced, resulting in increase in AUC (100%) and Cmax (88%) compared to age- matched volunteers with no renal impairment.

FOURTH FOLD

Hepatic Insufficiency: In volunteers with hepatic cirrhosis, sildenafil clearance was reduced, resulting in increase in AUC (84%) and Cmax (47%) compared to age- matched volunteers with no hepatic impairment.

INDICATION AND USE
Indicated for the treatment of erectile dysfunction in men.

RECOMMENDED DOSE:

Posology and method of administration
Sildenafil tablets are for oral administration.
Use in adults
For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. 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 daily dose is 100 mg. The maximum recommended dosing frequency is once per day.

Use in patients with impaired renal function
Dosage adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min). Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min), a 25 mg dose should be considered.

Use in patients with impaired hepatic function
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis), a 25 mg dose should be considered.
Use in patients using other medications
Given the extent of the interaction with patients receiving concomitant therapy with ritonavir (see Interaction with other medicinal products and other forms of interaction), it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48-hour period.
A starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP 3A4 inhibitors (e.g. erythromycin, saquinavir, ketoconazole, itraconazole). See section Interaction with other medicinal products and other forms of interaction. In order to minimize the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at lower doses should be considered (see section Special warnings and precautions for use and section Interaction with other medicinal products and other forms of interaction).

Use in children
Sildenafil is not indicated for use in children (<18 years old).

Use in elderly men
Dosage adjustments are not required in elderly patients.

MODE OF ADMINISTRATION:
Oral

CONTRAINDICATION:
Use of sildenafil is contraindicated in patients with a known hypersensitivity to any component of the tablet. Sildenafil is contraindicated in patients taking organic nitrates or nitric oxide donors, as this combination may lead to marked reduction in blood pressure that could prove fatal. Sildenafil is contraindicated in patients for whom sexual activity carries a major cardiovascular risk, in heart diseases affected by reduction in blood pressure, recent heart attacks, stroke, life threatening arrythymias, uncontrolled hypertension, unstable angina caused by cardiac failure and hypersentivity.

WARNING AND PRECAUTION:
General
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 shall consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.
Sildenafil 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 leukemia.
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.
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.

Women
Sildenafil is not indicated for use in women

FIRST FOLD

Fibre Direction

38.75 mm

105 mm

Pharma Code : XXXXX Mnl

Direction for Travel

BACK

Pediatrics
Sildenafil is not indicated in children

DRUG INTERACTIONS:

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 an increase in plasma sildenafil concentration when co-administered with sildenafil (50 mg) to healthy volunteers.
Stronger CYP3A4 inhibitor such as ketoconazole, itraconazole or mibefradil would be expected to have still greater effects, and population data from patients in clinical trials did indicate 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.
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 other diuretics, ACE inhibitors and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased by loop and potassium-sparing diurectics and 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 (IC50 >150 □M). Given sildenafil peak plasma concentrations of approximately 1 □M 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 (50mg) 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.
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.

PREGNANCY AND LACTATION

Pregnancy
Sildenafil is not indicated in pregnant women.

Lactation
Sildenafil is not indicated in nursing mothers.

SIDE EFFECTS:
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 sildenafil. 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 sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are directly related to sildenafil, to sexual activity, to the patients underlying cardiovascular disease, to a combination of these factors, or to other factors. Headache, flushing, dizziness, hypotension, angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, 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 intraocuular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema. Conjuctivitis, Photophobia, eye haemorrhage, cataract, dry eyes and eyes 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, accidential 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 leucopenia.
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 hyperthesia.
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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
As dizziness and altered vision were reported in clinical trials with Sildenafil, patients should exercise caution before driving, operating machinery or performing hazardous tasks.

OVERDOSAGE:
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, 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.

PRECLINICAL SAFETY DATA
Non-clinical studies revealed no special hazard for humans on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic and toxicity to reproduction.

PHARMACEUTICAL PARTICULARS

List of excipients
Sildenafil oral tablet contains the following Sodium Starch Glycolate, Povidone, Microcrystalline Cellulose, Ispropyl Alcohol, Purified Talc, Magnesium Stearate, Insta Moistshield Aqua II A22D20470 (Green).

Incompatibilities
Not applicable

STORAGE
Store at a temperature below 30 oC. Protect from light

SHELF LIFE
3 years

PRESENTATION
Alu/Clear PVC blister pack. A blister pack of 4 tablets (1x4)

MANUFACTURED IN INDIA BY
Ajanta Pharma Limited
Factory : B - 4/5/6, MIDC Area, Paithan 431 148.
Dist. Aurangabad, India.

PRODUCT REGISTRATION HOLDER
GoPharma Sdn Bhd ,
Selangor, Malaysia.

IMPORTED BY
Jetpharma Sdn Bhd
No.13, 1st Floor, Jalan Rajawali 2,
Bandar Puchong Jaya, 47100 Puchong,
Selangor, Malaysia.

DATE OF REVISION: February 2023

30XXXXX

ajanta pharma limited

Packaging Department

Name & Signature

Checked By : _____

Verified By : _____

Approved By : _____

Date : _____

For : Export Market | Co-ordinator Name : Prakash | Software : Corel Draw | Date : 16.02.2023

New Item Code : 30XXXXX | Item Type: Pack Insert | Artist Name : Vijay

Product Name : Kamagra 100 mg Tabs. | Earlier Item Code: P29069

Material : 40 gsm bible paper

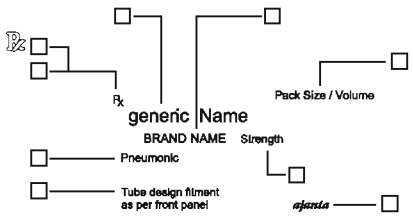
Actuel Size : 210 x 310 mm (FRONT + BACK) | Folding Size : 38.75 ± 105 mm | Varnish : Aqua

Print Repeat : NA | Drawing No. : PGB092113074LF

CMYK / Pantone : ☐ Black

Reason for Change : Pharmacode position changed. Address updated.

Front Panel:



Back Panel / Side Panel

Composition	☐	Barcode ▮▮▮▮	☐
Colour	☐	Warnings / Schedule H	☐
Dosage	☐	Caution / Schedule G	☐
Storage	☐	Statutory Contents	☐
Made in India	☐	Directions for use	☐
Company's Name	☐	Neutral code	☐
H.O.Address	☐	Factory + H.O.Address	☐
Factory Address	☐	Red line	☐
Toll Free No. / Email ID	☐	Other	☐

Side Panels

BRAND NAME ☐

PTN ☐ CKL ☐ CTGN ☐ LL ☐ TP ☐ DHJ ☐ GHT ☐ PMR ☐

Others:

Item Code	☐	Pharma Code	☐
LIF	☐	Colour Code	☐
Printed License No.	☐	Reference Sample	☐
O.P.Zone / DGFT	☐	Back-side Printing	☐
MOH approved a/w	☐	Change Parts	☐
		Buyer/IBM approval	☐

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