KIFARU 50 TABLETS
(Sildenafil Citrate Tablets 50mg)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KIFARU 50 TABLETS (Sildenafil Citrate Tablets 50mg)

STRENGTH

Sildenafil Citrate equivalent to Sildenafil…..50mg

PHARMACEUTICAL FORM

Tablets (Solid Oral)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chemical Name	Approved Name (if any)	Quantity per Tablet in mg	Active / Non - active
Piperazine,1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1Hpyrazolo[4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methyl-,2-hydroxy-1,2,3-propanetricarboxylate	Sildenafil Citrate IH equivalent to Sildenafil	71.6 ≡ 50.0	Active Ingredient

3. PHARMACEUTICAL FORM

Tablets (Solid Oral)

Blue colour, diamond shaped, uncoated tablets having 'K-50' embossed on one side and ‘SHALINA’ on the other side and free from any defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KIFARU 50 (Sildenafil Citrate Tablets 50mg) is used in the treatment of erectile dysfunction.

4.2 Posology and method of administration

Posology

The recommended dose is 50mg taken, as needed, approximately 1 hour before sexual activity. However, Kifaru may be taken anywhere from 4 hours to 0.5 hours before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100mg or decreased to 25mg. The maximum recommended dosing frequency is once per day.

Route of Administration: Oral

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway , sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

SILDENAFIL is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

The safety of sildenafil has not been studied in the following sub-groups of patients, and its use is therefore contraindicated: severe hepatic (blood pressure < 90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4.4 Special warnings and precautions for use

Cardiovascular effects: Carefully consider whether patients with certain underlying conditions (e.g., resting hypotension, fluid depletion) could be adversely affected by vasodilatory effects of sildenafil citrate. Not recommended in patients with pulmonary veno-occlusive disease.

Use with alpha-blockers: Note additive blood pressure-lowering effects. Bleeding: In patients with PAH secondary to CTD, higher rates of epistaxis with sildenafil citrate than placebo, including concomitant oral vitamin K antagonists.

Use with ritonavir and other potent CYP3A inhibitors: Coadministration not recommended.

Effects on the eye: Consider discontinuing sildenafil citrate if sudden loss of vision occurs, which could be non-arteritic ischemic optic neuropathy (NAION).

Hearing impairment: Discontinue sildenafil citrate if sudden decrease or loss of hearing occurs.

Use with PDE5 inhibitors: Avoid use with Kifaru or other PDE5 inhibitors.

Prolonged erection: Advise patients to seek emergency treatment if an erection lasts > 4 hours. Use sildenafil citrate with caution in patients predisposed to priapism.

Pulmonary hypertension secondary to sickle cell disease: Sildenafil citrate may cause serious vaso-occlusive crises.

Renal Impairment: No dose adjustments required (including severe impairment CLcr < 30 mL/min). **Hepatic Impairment:** Mild to moderate require no dose adjustment. Severe has not been studied.

Geriatric: No data in 65 yrs or older, In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or

other drug therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine: Increases plasma concentrations of sildenafil. Erythromycin: Increases AUC of sildenafil. Ritonavir: Increases AUC and Cmax of sildenafil. Saquinavir: Increases AUC and Cmax of sildenafil. Rifampin: Decreases plasma levels of sildenafil. Itraconazole: Increases plasma levels of sildenafil.

4.6 Fertility, Pregnancy and lactation

Not applicable as sildenafil is not indicated for women.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

The safety profile of Sildenafil is based on 9,570 patients in 74 double blind placebo-controlled clinical studies. 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, cyanopsia and blurred vision.

Adverse reactions from post-marketing surveillance have been gathered covering an estimated period >10 years. Because not all adverse reactions are reported to the Marketing Authorization Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org' .

4.9 Overdose

In studies with healthy volunteers of single doses up to 800mg, adverse events were similar to those seen at lower doses, but rates and severities 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction.

ATC Code: G04B E03.

5.1 Pharmacodynamic properties

Mechanism of action

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide 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 is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus

cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore, sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Pharmacodynamic effects

Studies in vitro have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

5.2 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 (25-100 mg).

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. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/mL (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Biotransformation

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 metabolised, with a terminal half life of approximately 4 h.

Elimination

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half life of 3-5 h. 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, 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 to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and Cmax of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance < 30 mL/min), sildenafil clearance was reduced, resulting in mean increases in AUC and Cmax of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased 79% and 200% respectively.

Hepatic insufficiency

In volunteers with mild to moderate 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. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose BP

Calcium Hydrogen Phosphate BP

Hydroxypropylcellulose BP

Maize starch BP

Sodium Benzoate BP

Purified Talc BP

Magnesium Stearate BP

Colloidal Anhydrous Silica BP

Croscarmellose Sodium BP

Hypromellose

Macrogols

Titanium Dioxide

Idealcoat Universal IJ-U-1028 (Hypromellose, Macrogols, Titanium Dioxide, FDC Blue)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months (3 Years)

6.4 Special precautions for storage

Do not store above 30°C. Protect from sunlight. Keep out of reach of children.

6.5 Nature and contents of container

Aluminium / PVC film blister.

KIFARU 50 is packed in a blister of 4 Tablets. 1 Such filled blister packed in a printed carton along with a leaflet.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS

SHALINA HEALTHCARE DMCC,

30th Floor, Almas Towers,

Jumeirah Lakes Towers Dubai-UAE.

Manufacturing Site Address:

SHALINA LABORATORIES PVT. LTD.

E-2 & E-3, M.I.D.C. Jejuri, Tal: Purandar, Dist.: Pune, Maharashtra, India

8. MARKETING AUTHORIZATION NUMBER

H2012/CTD337/373

9. DATE OF FIRST <REGISTRATION> /RENEWAL OF THE <REGISTARTION>

Date of first authorization: 6 Sep 2012

Date of latest renewal: Renewal application

10. DATE OF REVISION OF TEXT

Every two years

11. Dosimetry (If applicable)

Not Applicable

12. Instruction for preparation of Radio pharmaceuticals (If applicable)

Not Applicable