FRONT SIDE

adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was 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 not eliminated in the urine.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction.

ATC code: G04B E03.

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.

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 metabolized, 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 up to 126% and up to 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 by 200% and 79% 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.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

6 Pharmaceutical Particulars

6.1 List of excipients

Maize starch
Microcrystalline cellulose
Sodium Starch Glycolate
Colloidal anhydrous silica
Di-Calcium phosphate
Magnesium Stearate
Purified Talc
Croscarmellose Sodium
Polyethylene Glycol 6000
Titanium Dioxide
Lake Of Indigo Carmine
Hypromellose (5 cps)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months from the date of manufacture.

6.4. Special precautions for storage

Store at temperature not exceeding 30°C, protect from moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

1x4 Tablets in Alu-PVC Blister pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Manufactured by :

ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India

zim
Zeal & Innovation in Medicine

8. Marketing Authorization Number(S)

NA

9. Date of First Authorization/Renewal of the Authorization

NA

10. Date of Revision of the Text

02 Jul 2019

*PB381/X/XX/XX

Zimagra 100

Sildenafil Tablets USP 100 mg

1. Name of the Finished Pharmaceutical Product

1.1 Trade Name : ZIMAGRA 100 (Sildenafil Tablets USP 100 mg)

1.2 Strength : 100 mg

1.3 Pharmaceutical Form : *"Film Coated Tablets"*

2. Qualitative And Quantitative Composition

Each film coated tablet contains:
Sildenafil Citrate USP
Eq. to Sildenafil 100 mg
For full list of excipients, see section 6.1

3. Pharmaceutical Form

'Film coated tablet
Light blue, diamond shaped, film coated tablets engraved with "100" on one side and plain on other side.'

4. Clinical Particulars

4.1 Therapeutic indications

Sildenafil is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
In order for sildenafil to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology:

Use in adults

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, 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. If sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

Special populations

Elderly

Dosage adjustments are not required in elderly patients (≥ 65 years old).

Renal impairment

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 mL/min) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Hepatic impairment

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Paediatric population

Sildenafil is not indicated for individuals below 18 years of age.

Use in patients taking other medicinal products

With the exception of ritonavir for which co-administration with sildenafil is not advised a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors.
In order to minimise the potential of developing postural hypotension in patients receiving alpha-blocker treatment patients should be stabilized on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered.

Mode of Administration:

For oral use.

4.3 Contraindication

Hypersensitivity to the active substance or to any of the excipients used in formulation.
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

200 mm

210 mm

BACK SIDE

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 sildenafil is contraindicated in: severe hepatic impairment, hypotension (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 Phosphodiesterase).

4.4 Special warnings and special precautions for use
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.
Cardiovascular risk factors
Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.
Sildenafil potentiates the hypotensive effect of nitrates.
Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported association with the use of Sildenafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity.
Priapism
Agents for the treatment of erectile dysfunction, including 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 leukaemia).
Prolonged erections and priapism have been reported with sildenafil. In the event of an erection that persists for 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.
Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction
The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil, or other treatments for erectile dysfunction is not recommended.
Effects on vision
Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking sildenafil and consult a physician immediately.
Concomitant use with ritonavir
Co-administration of sildenafil with ritonavir is not advised.
Concomitant use with alpha-blockers
Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.
Effect on bleeding
Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro.
There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.
Women
Sildenafil is not indicated for use by women.

4.5 Interaction with other medicinal products and other forms of interaction
Effects of other medicinal products 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 and inducers of these isoenzymes may increase sildenafil clearance.
The pharmacokinetic analysis indicated a reduction in sildenafil clearance when coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine).
Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11- fold) increase in sildenafil plasma AUC.
The co-administration of sildenafil with ritonavir is not advised.
Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.
There was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, Cmax, tmax, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite.
Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg).
Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.
Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.
population pharmacokinetic analysis showed no effect of concomitant treatment on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).
In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and Cmax, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.
Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a serious interaction with sildenafil.
Effects of sildenafil on other medicinal products
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 µM). Sildenafil may alter the clearance of substrates of these isoenzymes.
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.
Riociguat: The additive systemic blood pressure lowering effect shows when PDE5 inhibitors were combined with riociguat.
Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals.
The alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50mg, or 100 mg) when administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5mmHg, respectively, were observed.
When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.
No significant interactions were shown when sildenafil (50 mg) was co-administered 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 acetyl salicylic acid (150 mg).
Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.
Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil treatment.
When sildenafil (100 mg) was coadministered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy 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.
In healthy male volunteers, sildenafil at steady state (80 mg t.i.d.) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan Cmax (125 mg b.i.d.).

4.6 Pregnancy and lactation
Sildenafil is not indicated for use by women.
There are no adequate and well-controlled studies in pregnant or breast-feeding women.
No relevant adverse effects 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 sildenafil in healthy volunteers.

4.7 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 Sildenafil, before driving or operating machinery.

4.8 Undesirable effects
Adverse reactions, defined as adverse events considered at least possibly related to Trimetazidine treatment are listed below using the following convention frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).
Very common: Headache,
Common: Dizziness, Visual colour distortions, Visual disturbance, Vision blurred, Flushing, Hot flush, Nasal congestion, Nausea, Dyspepsia.
Uncommon: Rhinitis, Hypersensitivity, Somnolence, Hypoaesthesia, Lacrimation disorders, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis, Vertigo, Tinnitus, Tachycardia, Palpitations, Hypertension, Hypotension, Epistaxis, Sinus Congestion, Gastro oesophageal reflux disease, Vomiting, Abdominal pain upper, Dry mouth, Rash, Myalgia, Pain in extremity, Haematuria, Chest pain, Fatigue, Feeling hot, Heart rate increased.
Rare: Cerebrovascular accident, Transient ischaemic attack, Seizure, Seizure recurrence, Syncope, Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discoloration, Deafness, Sudden cardiac death, Myocardial infarction, Ventricular arrhythmia, Atrial fibrillation, Unstable Angina, Throat tightness, Nasal oedema, Nasal dryness, Hypoaesthesia oral, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Penile haemorrhage, Priapism, Haematospermia, Erection increased, Irritability.

4.9 Overdose
In single dose up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of

200 mm
210 mm