1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of drug product

XFAYA Tablet 100 mg (Sildenafil Tablets 100 mg)

1.1 (Trade) name of product:

1.2 Strength

Each Film Coated Tablet Contains:

Sildenafil Citrate

Equivalent to Sildenafil…….100 mg

Excipient….....Q.S.

Approved colour used

1.3 Pharmaceutical Dosage Form

Tablets for oral administration

Product Name: XFAYA Tablet 100 mg (Sildenafil Tablets 100 mg)	
Dosage Form: Tablet	
Module 1 : Application Information	

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

XFAYA Tablet 100 mg (Sildenafil Tablets 100 mg)

Each Film Coated Tablet Contains:

Sildenafil Citrate

Equivalent to Sildenafil…….100 mg

Excipient .....Q.S.

Approved colour used

2.2 Quantitative Declaration

Batch Formula:

Batch Size: 100,000 Tablets

Sr. No	Ingredients	Grade	Rationale	Label Claim	Overages (%)	Quantity per Unit (mg)	Quantity per Batch (Actual-Kg)
	Mixing						
1.	Sidenafil Citrate	BP	Active	100 mg	-----	140.60mg	14.06
2.	Starch	BP	Diluent	-----	-----	15.47	1.547
3.	Lactose	BP	Diluent	-----	-----	11.87	1.187
4.	D.C.P. dihydrate	BP	flowing agent	-----	-----	93.06	9.306
5.	Sodium Starch Glycollate	BP	Disintegrant	-----	5%	30.0	3.000
	Binding						
6.	Starch	BP	Binder			15.00	1.500
7.	Polyvinyl pyrrolidone (PVPK-30)	BP	Vehicle	-----	-----	7.00	0.700
	Lubrication						
8.	Talc	BP	Lubricant	-----	-----	80.00	8.000
9.	Sodium Starch Glycollate	BP	Disintegrant	-----	-----	120.0	12.000
10.	Magnesium Stearate	BP	Lubricant	-----	-----	50.0	5.000
11.	Colloidal Silicon Dioxide	BP	Glidant	-----	-----	10.0	1.000
	Coating						
12.	Colour PONCEU 4R	IH	Colouring Agent	-----	-----	17.00	1.700

3. PHARMACEUTICAL DOSAGE FORM

Tablet for oral administration

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 50mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100mg or decreased to 25mg. 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 (see Section 5.2).

Special populations

Elderly

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

Renal impairment

The dosing recommendations described in "Use in adults" apply to 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 25mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50mg and 100mg as necessary.

Hepatic impairment

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25mg dose should be considered. Based on efficacy andtolerability, the dose may be increased step-wise to 50mg and 100mg 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 (see Section 4.4) a starting dose of 25mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors (see Section 4.5).

In order to minimise the potential of developing postural hypotension in patients receiving alpha-blocker treatment, patients should be stabilised on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see Sections 4.4 and 4.5).

Method of administration

For oral use.

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 (see Section 5.1), 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 guanylatecyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

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 (see section 4.4).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: 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 phosphodiesterases).

4.4 Special Warnings and 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 (see Section 5.1). 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 (see Section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of Sildenafil. Most, but not all, of these patients had pre-existing 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. It is not possible to determine whether these events are related directly to these factors or to other factors.

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 post-marketing experience. 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 (REVATIO), or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations 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 (see section 4.8). 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 (see section 4.8). Patients should be advised that in the event of any sudden visual defect, they should stop taking sildenafil and consult a physician immediately (see section 4.3).

Concomitant use with ritonavir

Co-administration of sildenafil with ritonavir is not advised (see Section 4.5).

Concomitant use with alpha-blockers

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see Section 4.5). 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 (see Section 4.2). 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.

The film coating of the Sildenafil tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

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

***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 and inducers of these isoenzymes may increase sildenafil clearance..

***In vivo* studies:**

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole,

erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500mg twice daily) with sildenafil (100mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200ng/ml, compared to approximately 5ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see Section 4.4) and in any event the maximum dose of sildenafil should under no circumstances exceed 25mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200mg three times a day) with sildenafil (100mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics (see Section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100mg dose of sildenafil was administered with erythromycin, a moderateCYP3A4 inhibitor, at steady state (500mg twice daily for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC, Cmax, Tmax, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50mg) to healthy volunteers.

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.

Although specific interaction studies were not conducted for all medicinal products, 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, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) 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 aserious interaction with sildenafil.

Effects of sildenafil on other medicinal products

***In vitro* studies:**

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that Sildenafil will alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

***In vivo* studies:**

Consistent with its known effects on the nitric oxide/cGMP pathway (see Section 5.1), 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 (see Section 4.3).

Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated (see section 4.3).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see Sections 4.2 and 4.4). In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, 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 4/5 mmHg, 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 (50mg) was co-administered with tolbutamide (250mg) or warfarin (40mg), both of which are metabolised by CYP2C9.

Sildenafil (50mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150mg).

Sildenafil (50mg) 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 compared to placebo treatment. In a specific interaction study, where sildenafil (100mg) was co-administered 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 (see Section 5.1).

Sildenafil (100mg) 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 bosentanCmax (125 mg b.i.d.).

4.6 Fertility, pregnancy and lactation

Sildenafil is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breastfeeding 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 (see section 5.1).

4.7 Effects on ability to drive and operate machine

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

Summary of the safety profile

The safety profile of Sildenafil is based on 9570 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 vision blurred. Adverse reactions from post-marketing surveillance has been gathered covering an estimated period>10 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

Tabulated list of adverse reactions

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance

System Organ Class	Very common *(≥ 1/10)*	Common *(≥ 1/100 and <1/10)*	Uncommon *(≥ 1/1000 and <1/100)*	Rare *(≥ 1/10000 and <1/1000)*
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure,* Seizure recurrence,* Syncope

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Eye disorders		Visual colour distortions**, Visual disturbance, Vision blurred	Lacrimation disorders***, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis	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
Ear and labyrinth disorders			Vertigo, Tinnitus	Deafness
Cardiac disorders			Tachycardia, Palpitations	Sudden cardiac death,* Myocardial infarction, Ventricular arrhythmia,* Atrial fibrillation, Unstable angina
Vascular disorders		Flushing, Hot flush	Hypertension, Hypotension	

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Respiratory, thoracic and mediastinal disorders		Nasal congestion	Epistaxis, Sinus congestion	Throat tightness, Nasal oedema, Nasal dryness
Gastrointestinal disorders		Nausea, Dyspepsia	Gastro oesophageal reflux disease, Vomiting, Abdominal pain upper, Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	Stevens-Johnson Syndrome (SJS),* Toxic Epidermal Necrolysis (TEN)*
Musculoskeletal and connective tissue disorders			Myalgia, Pain in extremity	
Renal and urinary disorders			Haematuria	
Reproductive system and breast disorders				Penile haemorrhage, Priapism,* Haematospermia, Erection increased
General disorders and administration site conditions			Chest pain, Fatigue, Feeling hot	Irritability
Investigations			Heart rate increased	

*Reported during post-marketing surveillance only

Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythropsia and Xanthopsia*Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation increased

4.9 Overdose

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

Clinical efficacy and safety

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100mg in healthy volunteers produced no clinically relevant effects on ECG.

In a study of the hemodynamic effects of a single oral 100mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (>70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 7% and 6% respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9%. Sildenafil showed no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries.

A double-blind, placebo-controlled exercise stress trial evaluated 144 patients with erectile dysfunction and chronic stable angina who regularly received anti-anginal medicinal products (except nitrates). The results demonstrated no clinically relevant differences between sildenafil and placebo in time to limiting angina.

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast

sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100mg) demonstrated no significant changes in visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photostress).
There was no effect on sperm motility or morphology after single 100mg oral doses of sildenafil in healthy volunteers (see section 4.6)..
Further information on clinical trials

In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see Section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25mg), 74% (50mg) and 82% (100mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.

Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long term studies.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Sildenafil in all subsets of the paediatric population for the treatment of erectile dysfunction. See 4.2 for information on paediatric use.

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 (25-100mg).

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 (100mg single dose), less than 0.0002% (average 188ng) 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 50mg 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. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

5.3 Pre-clinical 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

Starch

Lactose

D.C.P. dihydrate

Sodium Starch Glycollate

Starch

Polyvinyl pyrrolidone (PVPK-30)

Talc

Magnesium Stearate

Colloidal Silicon Dioxide

Colour PONCEU 4R

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

36 months from the date of manufacture.

6.3 Special Precautions for Storage

Store below 30°C. Protect from light.

6.4 Nature and Contents of Container

Alu/PVC blister with 5 Tablets.

6.5 MANUFACTURE/APPLICANT:

Kashmik Formulation Pvt. Ltd.,

PF 13, Opp. Procter and Gamble,

Bol GIDC 2, Sanand, Ahmedabad – 382 170,

Gujarat, India.

7. Marketing authorisation holder:

LIRICON PHARMACEUTICAL LTD.,
Nigeria.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text