SUMMARY OF PRODUCT CHARACTERISTICS

EDEFIL 50/100
(Sildenafil Citrate Tablet 50/100 mg)

1. NAME OF THE MEDICINAL PRODUCT

EDEFIL 50/100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film coated tablet

Description:
Edefil 50: Red coloured, rounded triangular shaped, film-coated tablets, with 'S22' engraved on one side and plain on the other side.

Edefil 100: Red coloured, rounded triangular shaped, film-coated tablets, with 'S23' engraved on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sildenafil tablets 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 citrate to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology
Dose

<u>Use in adults</u>
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 citrate 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 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 citrate 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 25 mg 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 has been reported 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 (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 citrate 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. 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 citrate 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 citrate. 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 citrate 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, 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 citrate 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 co-administration 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 reported 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil

Reported 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.

Reported in vivo studies
Reduction in sildenafil clearance has been reported with co-administration of CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was reported in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25 mg should be considered.

It has been reported that 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 C_{max} and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil have been reported to be approximately 200 ng/mL, compared to approximately 5 ng/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 25 mg within 48 hours.

It has been reported that co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} 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 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg twice daily for 5 days), 182% increase in sildenafil systemic exposure (AUC) has been reported. In normal healthy male volunteers, there was no reported evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max}, t_{max}, 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, has been reported to cause a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) 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.

Population pharmacokinetic analysis reported 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 reported 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 C_{max}, 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

Reported in vitro studies
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50}>150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that sildenafil citrate will alter the clearance of substrates of these isoenzymes.

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

Reported in vivo studies
Consistent with its known effects on the nitric oxide/cGMP pathway (see **section 5.1**), sildenafil was reported 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: Pre-clinical studies reported additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been reported to augment the hypotensive effects of PDE5 inhibitors. There was no reported evidence of reported 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 reported 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. 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 reported in these study populations. 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 reported when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised 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, reported no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific reported interaction study, where sildenafil (100 mg) 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 reported 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.) reported 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg b.i.d.).

4.6 Fertility, pregnancy and lactation

Sildenafil citrate is not indicated for use by women.

There are no adequate and well-controlled studies reported in pregnant or breast-feeding women.

No relevant adverse effects have been reported in reproduction studies in rats and rabbits following oral administration of sildenafil.

No effect on sperm motility or morphology has been reported after single 100 mg oral doses of sildenafil in healthy volunteers.

4.7 Effects on ability to drive and use machines

Sildenafil citrate may have a minor influence on the ability to drive and use machines.

As dizziness and altered vision were reported in clinical studies with sildenafil, patients should be aware of how they react to sildenafil citrate, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated list of adverse reactions

In the table below all medically important adverse reactions, which were reported in clinical studies 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: 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** ***(≥ 1/1,000 and <1/100)***	**Rare** ***(≥ 1/10,000 and <1/1,000)***
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure*, Seizure recurrence*, Syncope
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,

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 and <1/10)	Uncommon (≥ 1/1,000 and <1/100)	Rare (≥ 1/10,000 and <1/1,000)
				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	
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			Chest pain, Fatigue, Feeling hot	Irritability

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 and <1/10)	Uncommon (≥ 1/1,000 and <1/100)	Rare (≥ 1/10,000 and <1/1,000)
administration site conditions				
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 reported single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those reported 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 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
In vitro studies have reported 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 Pharmacokinetics

Absorption
Sildenafil is rapidly absorbed. Maximum reported 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 reported to be 41% (range 25-63%). After oral dosing of sildenafil AUC and C_{max} are reported to increase in proportion with dose over the recommended dose range (25-100 mg).

When sildenafil is taken with food, the rate of absorption is reported to be reduced with a mean delay in t_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Distribution
The mean steady state volume of distribution (V_d) for sildenafil is reported to be 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is reported to be 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 has been reported to be 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 reported for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h.

<u>*Elimination*</u>

The total body clearance of sildenafil is reported to be 41 L/h with a resultant terminal phase half-life of 3-5 h. After either oral or intravenous administration, sildenafil is reported to be 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

<u>*Elderly*</u>

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 reported in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration has been reported to be approximately 40%.

<u>*Renal insufficiency*</u>

In volunteers with mild to moderate renal impairment (creatinine clearance=30-80 mL/min), the pharmacokinetics of sildenafil was not reported to be altered after receiving a 50 mg single oral dose. The mean AUC and C_{max} of the N-desmethyl metabolite reportedly 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 reported to be reduced, resulting in mean increases in AUC and C_{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were reported to be significantly increased by 200% and 79% respectively.

<u>*Hepatic insufficiency*</u>

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reported to be reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been reported.

5.3 Preclinical safety data

Non-clinical data reported 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

Microcrystalline Cellulose, Croscarmellose Sodium, Anhydrous Calcium Hydrogen Phosphate, Magnesium Stearate & Opadry Red 06B 55000.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperature not exceeding 30°C, protected from moisture.

6.5 Nature and contents of container

PVC blisters of 4 tablets. Such 1 blister packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

RANBAXY NIGERIA LIMITED

8. MARKETING AUTHORISATION NUMBER(S)

B4-8459 (50 mg), B4-8460 (100 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/04/2018

10. DATE OF REVISION OF THE TEXT

August 2022

REFERENCES

1. Summary of product characteristics of *VIAGRA 25, 50, 100 mg*; Upjohn UK Limited, January 2021.

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