PACKAGE INSERT

Sildenafil 50 mg film-coated Tablets (SYNERRV SILDENAFIL)
Sildenafil 100 mg film-coated Tablets (SYNERRV SILDENAFIL)

NAME AND STRENGTH OF ACTIVE INGREDIENTS:
Sildenafil citrate Ph. Eur. eq. to Sildenafil 50 mg
Sildenafil citrate Ph. Eur. eq. to Sildenafil 100 mg

PRODUCT DESCRIPTION:
50 mg Tablet: Pale blue to blue, 13.2 X 5.5 mm capsule shaped film-coated tablet, debossed with 'SL50' on one side and plain on other side.

100 mg Tablet: Pale blue to blue, 16.5 X 7.5 mm capsule shaped film-coated tablet, debossed with 'SL100' on one side and plain on other side.

THERAPEUTIC INDICATIONS:
Sildenafil Tablet is indicated for use in adult men with erectile dysfunction, which is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.
In order for Sildenafil Tablet to be effective, sexual stimulation is required.

POSOLOGY AND METHOD OF ADMINISTRATION
Sildenafil tablets are for oral administration.

Use in adults
Film-coated tablets
For most patients, the recommended dose is 50 mg taken, as needed approximately 1 hour before sexual activity.

Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended daily dose is 100 mg. The maximum recommended dosing frequency is once per day.

Use in patients with impaired renal function
Dosage adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 mL/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min), a 25 mg dose should be considered.

Use in patients with impaired hepatic function
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g., cirrhosis), a 25 mg dose should be considered.

Use in patients using other medications
Given the extent of the interaction with patients receiving concomitant therapy with ritonavir (see section Interaction With Other Medicinal Products), co-administration with ritonavir is not

advised. If ritonavir is co-administered with sildenafil, it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48-hour period.

A starting dose of 25 mg should be considered in patients receiving concomitant treatment with the CYP3A4 inhibitors (e.g., erythromycin, saquinavir, ketoconazole, itraconazole). See section Interaction With Other Medicinal Products.

In order to minimize the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at lower doses should be considered (see section Warning and Precautions & section Interaction With Other Medicinal Products).

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

Use in elderly men
Since sildenafil clearance is reduced in elderly patients, a first dose of 25 mg should be considered.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.
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.
Medicines 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 Tablet 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 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).

WARNING AND PRECAUTIONS
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 Tablet 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 post-marketing in temporal association with the use of Sildenafil Tablet. 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 Tablet 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
Non-arteritic anterior ischemic optic neuropathy (NAION),, a rare condition and a cause of decreased vision or loss of vision, has been reported rarely post-marketing with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors such as low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 5 half-life of PDE5 inhibitor use. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 males aged ≥50 per year in the general population. In case of sudden visual loss, patients should be advised to stop taking sildenafil and consult a physician immediately.
Individuals who have already experienced NAION are at increased risk of NAION recurrence. PDE5 inhibitors, including sildenafil, should not be used in these patients.
A minority of patients with the inherited condition retinitis pigmentosa have genetic disorders of retinal phosphodiesterases. There is no safety information on the administration of sildenafil to patients with retinitis pigmentosa, therefore, sildenafil should be administered with caution to these patients.
Effect on hearing

Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing patients should be advised to stop taking sildenafil and consult a physician promptly.

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.

Lactose Intolerance

The film coating of the tablet contains lactose. Sildenafil Tablet should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Women

Sildenafil Tablet is not indicated for use by women.

Concomitant use with ritonavir

Given the extent of the interaction with patients receiving concomitant therapy with ritonavir (see section Interaction With Other Medicinal Products), co-administration with ritonavir is not advised. If ritonavir is co-administered with sildenafil, it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48-hour period.

INTERACTION WITH OTHER MEDICINAL PRODUCTS:

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 25 mg should be considered.

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. At 24 hours, the plasma levels of sildenafil were still 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 and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.
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. 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), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no 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, caused 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.
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 C_{max}, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.
<u>Effects of sildenafil on other medicinal products</u>
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 tablets 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
Sildenafil was shown to potentiate the hypotensive effect of acute and chronic nitrates. Therefore, use of nitric oxide donors, organic nitrates, or organic nitrites in any form either regularly or intermittently with sildenafil is contraindicated. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. 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 (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 hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.
In a specific 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 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 C_{max} (125 mg b.i.d.).

PREGNANCY AND LACTATION
Sildenafil is not indicated for use in women.

No teratogenic effects, impairment of fertility or adverse effects on peri-/post-natal development were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

There are no adequate and well-controlled studies in pregnant or lactating women.

SIDE EFFECTS
The adverse events were generally transient and mild to moderate in nature.

In fixed-dose studies, the incidence of some adverse events increased with dose.

The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.

The most commonly reported adverse reactions were headache and flushing.

Adverse reactions reported in clinical trials and post-marketing surveillance are presented in Table 1 below:

Table 1 ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC:

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 and <1/10)**	**Uncommon (≥1/1000 and <1/100)**	**Rare (≥ 1/10,000 and <1/1000)**
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence	Seizure*; Seizure recurrence*; Syncope
Eye disorders		Vision blurred; Visual disturbance; Cyanopsia	Eye pain; Photophobia; Photopsia; Chromatopsia; Ocular hyperaemia; Visual brightness	Eye oedema; Eye swelling; Dry eye; Asthenopia; Halo vision; Xanthopsia; Erythropsia; Eye disorder; Conjunctival hyperaemia; Eye irritation; Abnormal sensation in eye; Eyelid oedema
Cardiac disorders			Tachycardia; Palpitations	
Vascular disorders		Hot flush; Flushing	Hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Epistaxis; Sinus congestion	Throat tightness; Nasal dryness; Nasal oedema
Gastrointestinal disorders		Nausea; Dyspepsia	Gastro oesophagael reflux disease; Vomiting; Abdominal pain upper; Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	

Musculoskeletal and connective tissue disorders			Myalgia; Pain in extremity	
Reproductive system and breast disorders				Priapism*; Erection increased
General disorders and administration site conditions			Feeling hot	Irritability
Investigations			Heart rate increased	

* ADR identified post-marketing.

At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

In an analysis of double-blind placebo-controlled clinical trials encompassing over 700 person-years of observation on placebo and over 1300 person-years on sildenafil, there were no differences in the incidence rate of myocardial infarction (MI) or in the rate of cardiovascular mortality for patients receiving sildenafil compared to those receiving placebo. The rates of MI were 1.1 per 100 person-years for men receiving sildenafil and for those receiving placebo. The rates of cardiovascular mortality were 0.3 per 100 person-years for men receiving sildenafil and those receiving placebo.

PHARMACOLOGICAL PROPERTIES:
PHARMACODYNAMICS PROPERTIES:
Sildenafil, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Mechanism of Action: The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation.

NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum.

When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

Sildenafil at recommended doses has no effect in the absence of sexual stimulation. Studies *in* vitro have shown that sildenafil is selective for PDE5.

Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE 6, >80-fold for PDE1, >700-fold for PDE2, PDE3, and PDE4, PDE7 – PDE11).

The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility.

Clinical studies

Cardiac
Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing was 8.3 mmHg. The corresponding change in supine diastolic blood pressure was 5.3 mmHg.

Larger but similarly transient effects on blood pressure were recorded among patients receiving concomitant nitrates (see section Contraindication and section Interaction With Other Medicinal Products).

In a study of the hemodynamic effects of a single oral 100 mg 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, and resulted in improvement (approximately 13%) in adenosine-induced coronary flow reserve (in both stenosed and reference arteries).

In a double-blind, placebo-controlled trial, 144 patients with erectile dysfunction and stable angina, who were taking their regular antianginal medications (except nitrates) were exercised until limiting angina occurred. The duration of treadmill exercise was statistically significantly longer (19.9 seconds; 95% confidence interval:
0.9 - 38.9 seconds) in the evaluable patients who had taken a single dose of sildenafil 100 mg compared to patients who had taken a single dose of placebo. The mean exercise times (adjusted for baseline) to the onset of limiting angina were 423.6 and
403.7 seconds for sildenafil and placebo, respectively.

A randomized, double-blind, placebo-controlled, flexible-dose study (sildenafil up to 100 mg) in males (N=568) with erectile dysfunction and arterial hypertension taking two or more antihypertensive agents was conducted. Sildenafil improved the erections in 71% of men compared to 18% in the placebo group, and 62% of attempts at sexual intercourse were successful with sildenafil compared to 26% on placebo. The incidence of adverse events was consistent with observations in other patient populations, as well as in the subjects taking three or more antihypertensive agents.

Visual

Mild and transient differences in color discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 60 minutes following a 100 mg dose, with no effects evident after 120 minutes 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. In vitro studies show that sildenafil is 10-fold less potent against PDE6 than PDE5. Sildenafil has no effect on visual acuity, contrast sensitivity, electroretinograms, intraocular pressure, or pupillometry.

In a placebo-controlled, crossover study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100 mg) was well-tolerated and demonstrated no clinically significant changes in the visual tests conducted (visual acuity, Amsler grid, color discrimination, simulated traffic light, Humphrey perimeter and photostress).

Efficacy
The efficacy and safety of sildenafil was evaluated in 21 randomized, double-blind, placebo-controlled trials of up to 6 months duration. Sildenafil was administered to more than 3000 patients aged 19-87, with ED of various etiologies (organic, psychogenic, mixed). The efficacy was evaluated by global assessment question, diary of erections, the International Index of Erectile Function (IIEF, a validated sexual function questionnaire) and a partner questionnaire.

Sildenafil efficacy, determined as the ability to achieve and maintain an erection sufficient for sexual intercourse, was demonstrated in all 21 studies and was maintained in long-term extension studies (one year). In fixed-dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg) and 82% (100 mg) compared to 25% on placebo. In addition to improvements in erectile dysfunction, analysis of the IIEF showed that sildenafil treatment also improved the domains of orgasm, satisfaction with intercourse and overall satisfaction.

Across all trials, the proportions of patients reporting improvement on sildenafil were 59% of diabetic patients, 43% of radical prostatectomy patients and 83% of patients with spinal cord injury (versus 16%, 15% and 12% on placebo, respectively).

PHARMACOKINETICS PROPERTIES:
Sildenafil pharmacokinetics are dose-proportional over the recommended dose range.

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 C_{max} 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 t_{max} of 60 minutes and a mean reduction in C_{max} of 29%.
Distribution
The mean steady-state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations. Based upon measurements of sildenafil in semen of healthy volunteers 90

minutes after dosing, less than 0.0002% (average 188 ng) of the administered dose may appear in the semen of patients.

Biotransformation

It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. 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 (creatinine clearance= 50-80 mL/min) and moderate (creatinine clearance = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered.

In volunteers with severe (creatinine clearance≤30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC (100%) and Cmax (88%) compared to age-matched volunteers with no renal impairment (see section Posology And Method Of Administration).

In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased 200% and 79% respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic Insufficiency

In volunteers with hepatic cirrhosis (Child-Pugh class A and B), sildenafil clearance was reduced, resulting in increases in AUC (85%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment (see section Posology And Method Of Administration). The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh class C) have not been studied.

OVERDOSE

In single dose volunteer studies of doses 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 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.

INCOMPATIBILITIES: Not Applicable

STORAGE: Store below 30ºC.

EXCIPIENTS: Tablet core: microcrystalline cellulose, croscarmellose sodium, silica, colloidal anhydrous, magnesium stearate, calcium hydrogen phosphate anhydrous,
Opadry® II complete Film coating system 31K60715 Blue: lactose monohydrate, hydroxypropylmethyl cellulose, titanium dioxide, triacetin, indigo carmine aluminium lake.

SHELF LIFE: 24 month

PRESENTATION: Aluminium / PVC Blister, Carton of 4 tablets and 28 tablets.

Manufactured for:
SYNERRV (S) PTE. LTD.
100 Jalan Sultan,
#09-06 Sultan Plaza,
Singapore (199001).

Manufactured By:
Umedica Laboratories Pvt. Ltd.,
Plot No. 221, IInd Phase, GIDC,
Vapi – 396 195, Gujarat, India.

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