Sildenafil Tablets IP

VIAGRA®

1. TRADE NAME OF THE MEDICINAL PRODUCT

VIAGRA®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sildenafil citrate IP equivalent to 25, 50 or 100 mg sildenafil.

For the full list of excipients (see section 6.1).

All presentations/strengths/pack sizes may not be marketed.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, rounded, diamond-shaped film-coated, tablets equivalent to 25 mg, 50 mg or 100 mg of sildenafil for oral administration, marked “PFIZER” on one side, and “VGR 25”, “VGR 50” or “VGR 100” on the other.

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.

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Licensed user: Pfizer Limited, India.

4.2 Posology and method of administration

Posology

Use in adults

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity.

Based on efficacy and tolerability, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2 **Pharmacokinetic properties**).

Special populations

Renal impairment

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. Based on efficacy and tolerability the dose may be increased stepwise 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 stepwise to 50 mg up to 100 mg as necessary.

Use in patients taking other medicinal products

Given the extent of the interaction with patients receiving concomitant therapy with ritonavir (see section 4.5 **Interaction with other medicinal products and other forms of interaction**), 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 4.5 **Interaction with other medicinal products and other forms of interaction**).

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 section 4.4 **Special warnings and precautions for use** and section 4.5 **Interaction with other medicinal products and other forms of interaction**).

Paediatric population

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

Elderly

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

Method of administration

For oral use.

4.3 Contraindications

Use of sildenafil is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1 **List of excipients**.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1 **Pharmacodynamic properties**), sildenafil was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its administration to patients who are concurrently using nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently is therefore contraindicated (see section 4.5 **Interaction with other medicinal products and other forms of interaction**).

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 **Interaction with other medicinal products and other forms of interaction**).

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 **Special warnings and precautions for use**).

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 thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.

Cardiovascular risk factors

There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

Agents for the treatment of erectile dysfunction should not be used in men for whom sexual activity is inadvisable.

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage and transient ischaemic attack hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil for erectile dysfunction. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

In clinical trials, sildenafil has been shown to have systemic vasodilatory properties, resulting in mild and transient decreases in blood pressure (see section 5.1 **Pharmacodynamic properties**). This is of little or no consequence in most patients. However, 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 **Contraindications**).

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 **Undesirable effects**). 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 **Undesirable effects**). 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 **Contraindications**).

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. Therefore physicians should discuss this risk with these patients and whether they could be adversely affected by use of PDE5 inhibitors. PDE5 inhibitors, including sildenafil, should be used with caution in these patients and only when the anticipated benefits outweigh the risks.

Concomitant use with ritonavir

Co-administration of sildenafil with ritonavir is not advised (see section 4.5 **Interaction with other medicinal products and other forms of interaction**).

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 **Interaction with other medicinal products and other forms of interaction**). 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 **Posology and method of administration**). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

Use in patients with *retinitis pigmentosa*

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 bleeding

In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). 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.

Priapism

Agents for the treatment of erectile dysfunction 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 anemia, 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 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, and the use of such combinations is not recommended.

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.

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

Women

VIAGRA 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).

Cimetidine (800 mg), a cytochrome P450 inhibitor and a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.

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 addition, co-administration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady-state (1200 mg three times daily) 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 affect on saquinavir pharmacokinetics (see section 4.2 **Posology and method of administration**). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

Co-administration with 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 1000% (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 dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics (see section 4.2 **Posology and method of administration**). Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see section 4.4 **Special warnings and precautions for use**) and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.

When the dose of sildenafil for subjects receiving potent CYP3A4 inhibitors was administered as recommended, the maximum free plasma sildenafil concentration did not exceed 200 nM for any individual and was consistently well tolerated. Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of 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 (ACE) 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.

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 major circulating metabolite.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels 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

***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 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 **Pharmacodynamic properties**); 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 (see section 4.3 **Contraindications**).

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 **Contraindications**).

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) stabilised 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 stabilised on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see section 4.2 **Posology and method of administration** and section 4.4 **Special warnings and precautions for use**).

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 (100 mg) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates (see above, **Effects of other medicinal products on sildenafil**).

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.).

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

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08% (80 mg/dL).

No interaction was seen when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Analysis of the safety database showed no difference in the side effect profile in patients taking sildenafil with and without antihypertensive medication.

4.6 Fertility, pregnancy and lactation

Sildenafil is not indicated for use in women.

There are no adequate and well-controlled studies in pregnant or lactating 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 was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 5.1 **Pharmacodynamic properties**).

4.7 Effects on ability to drive and use machines

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

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 9,570 patients in 74 double-blind placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and 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 (≥1/1000 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 (≥1/10,000 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
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

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)
				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

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)
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.

The following adverse reactions were reported during post-marketing surveillance:

Immune system disorders: hypersensitivity reaction (including skin rash).

Nervous system disorders: seizure, seizure recurrence.

Cardiac disorders: tachycardia.

Vascular disorders: hypotension, syncope, epistaxis.

Gastrointestinal disorders: vomiting.

Eye disorders: eye pain, red eyes/bloodshot eyes.

Reproductive system and breast disorders: prolonged erection and/or priapism.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but 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 it is not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.

Pharmacodynamic effects:
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 PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, and PDE4, PDE7-PDE11).

The approximately 4000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in 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.

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 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg.

Larger but similarly transient effect on blood pressure were recorded among patients receiving concomitant nitrates (see section 4.3 **Contraindications** and section 4.5 **Interactions with other medicinal products and other forms of interaction**).

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).

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.

A randomised, 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 colour 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, colour discrimination, simulated traffic light, Humphrey perimeter and photostress).

Efficacy

In clinical trials sildenafil was administered to more than 8,000 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 **Contraindications**).

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 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.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 4.6 **Fertility, pregnancy and lactation**).

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 section 4.2 **Posology and method of administration**) for information on paediatric use.

5.2 Pharmacokinetic properties

Sildenafil pharmacokinetics are dose-proportional over the recommended dose range.

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.

Absorption
Sildenafil is rapidly absorbed after oral administration, with mean absolute bioavailability of about 41% (range 25%-63%).

Sildenafil inhibits the human PDE5 enzyme *in vitro* by 50% at a concentration of 3.5 nM. In man, the mean maximum free plasma concentration of sildenafil following a single oral dose of 100 mg is approximately 18 ng/mL, or 38 nM.

Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state.

When sildenafil is taken with a high fat meal, 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%, however, the extent of absorption was not significantly affected (AUC decreased by 11%).

Distribution
The mean steady-state volume of distribution (V_{ss}) 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 are both approximately 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.

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
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes.

The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolised.

This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug.

In healthy volunteers, 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 hours.

Elimination
The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the 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. The mean AUC and C_{max} 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 (creatinine clearance <30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC (100%) and C_{max} (88%) compared to age-matched volunteers with no renal impairment (see section 4.2 **Posology and method of administration**).

In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased by 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 A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with

no hepatic impairment (see section 4.2 **Posology and method of administration**). The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh class C) has not been studied.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose (hypromellose), titanium dioxide (E171), lactose, triacetin and indigo carmine aluminium lake (E132).

Excipient with known effect:
Each 25 mg film-coated tablet contains 0.834 mg lactose (as monohydrate).
Each 50 mg film-coated tablet contains 1.667 mg lactose (as monohydrate).
Each 100 mg film-coated tablet contains 3.334 mg lactose (as monohydrate).

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

5 years

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.

6.5 Nature and contents of container

Clear PVC 250 μm blister pack of 1 and/or 2 tablets.

6.6 Instruction for use and handling

No special instructions.