פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA® 25 mg

VIAGRA®50 mg

VIAGRA®100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIAGRA® 25 mg: Each tablet contains sildenafil (as citrate)
VIAGRA® 50 mg: Each tablet contains sildenafil (as citrate)
VIAGRA® 100 mg: Each tablet contains sildenafil (as citrate)
For the full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

The 25 mg tablets are blue film coated, rounded diamond-shaped tablets, marked PFIZER on one side and VGR 25 on the other.
The 50 mg tablets are blue film coated, rounded diamond-shaped tablets, marked PFIZER on one side and VGR 50 on the other.
The 100 mg tablets are blue film coated, rounded diamond-shaped tablets, marked PFIZER on one side and VGR 100 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIAGRA is indicated for the treatment of erectile dysfunction.

4.2 Posology and method of administration

Sildenafil tablets are for oral administration.

Use in adults

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, 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 Viagra 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).

R*enal 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 toleration, the dose may be increased to 50 mg and 100 mg as necessary.

H*epatic 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 toleration, the dose may be increased step-wise to 50 mg and 100 mg as necessary.

Paediatric population:

Viagra® is not indicated for individuals below 18 years of age.

Use in patients using other medications

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 for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see sections 4.4 and 4.5).

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

The co-administration of PDE5 inhibitors, including sildenafil, with 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).

Viagra® 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 special precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, before pharmacological treatment is considered.

Cardiovascular risk factors

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

Sildenafil has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.3/5.3 mmHg, see 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.
There is no controlled clinical data on the safety or efficacy of sildenafil in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life threatening arrhythmia within the last 6 months.
- Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110).
- Patients with cardiac failure or coronary artery disease causing unstable angina.

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 anaemia, multiple myeloma or leukaemia).
Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists for longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil (REVATIO), or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

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

Viagra® potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina , sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage and transient ischemic 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.

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5 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 minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at lower doses 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.

Sildenafil has no effect on bleeding time, including during co-administration with aspirin.

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

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 Pfizer and consult a physician immediately (see section 4.3).

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

Sudden decrease or loss of hearing has been reported in a small number of postmarketing 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 Sildenafil tablet contains lactose. Sildenafil should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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). 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.

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.

Coadministration 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 Cmax 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 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.

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

When a single 100 mg dose of sildenafil was administered with erythromycin, a specific 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

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

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.

Although specific interaction studies were not conducted for all medicinal products, Population pharmacokinetic analysis showed no effect of concomitant medication 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 (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.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.
Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability 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, Cmax, Tmax, elimination rate constant, or subsequent half-life of sildenafil or its major circulating metabolite.

Effects of sildenafil on other medicinal products

In vitro studies:
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of

approximately 1 µM after recommended doses, it is unlikely that sildenafilwill 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 effects 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 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).

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 lightheadedness, but not syncope.
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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for Use).

No significant interactions were shown when sildenafil (50mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

Sildenafil (100 mg) did not effect 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.).

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

Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy

volunteers with mean maximum blood alcohol levels of 80 mg/dL.

Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. 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 (see section 5.1).

Analysis of the safety data base showed no difference in the side effect profile in patients taking sildenafil with and without anti-hypertensive 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 breast-feeding women.

No teratogenic effects, impairment of fertility or adverse effects on peri/postnatal 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 sildenafilin healthy volunteers.

4.7 Effects on ability to drive and use machines

The effect of sildenafil on the ability to drive and use machinery has not been studied

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

4.8 Undesirable effects

The safety profile of Viagra® is based on 9570 patients in 74 double blind placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness nausea, hot flush, visual disturbance, cyanopsia and blurred vision

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.

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

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

System Organ Class	**Very common** ***(≥ 1/10)***	**Common** ***(≥ 1/100 and <1/10)***	**Uncommon** ***(≥ 1/1000 and <1/100)***	**Rare** ***(≥ 1/10000 and <1/1000)***	
			Dry mouth		
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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

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 not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction
Pharmacotherapeutic group: ATC Code G04B E03

Mechanism of action
Sildenafil is a novel oral therapy for erectile dysfunction which restores impaired erectile function by increasing blood flow to the penis, resulting in a natural response to sexual stimulation.

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) which is responsible for degradation of cGMP in the corpus cavernosum. 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 beneficial pharmacological effects.

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects.
The mean maximum decreases in supine systolic blood pressure following 100 mg oral

dosing was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle.

In a study of the hemodynamic effects of a single oral 100mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreases by 7% and 6%,respectively compared to baseline.Mean pulmonary systolic blood pressure decreases 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 randomized, double-blind, placebo-controlled, flexible-dose study (sildenafil up to 100mg) 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.

No clinical relevant differences were demonstrated in time to limiting angina for sildenafil when compared with placebo in a double blind, placebo controlled exercise stress trial in 144 patients with erectile dysfunction and chronic stable angina, who were taking on a regular basis anti-anginal medications (except nitrates).

Sildenafil has no effect on visual acuity or contrast sensitivity. Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100 mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. *In vitro* studies show that sildenafil is 10-fold less potent against PDE6 than PDE5.

Pharmacodynamic effects
Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Clinical efficacy and safety

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

In a placebo-controlled, crossover study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100mg) 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).

5.1.1 Further information on clinical trials

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

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (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.

5.2 Pharmacokinetic properties

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

It is eliminated predominantly by hepatic metabolism (mainly cytochrome P4503A4) and is converted to an active metabolite with properties similar to the parent, sildenafil.

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.

After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM).

Protein binding is independent of total drug concentrations.

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 metabolized.

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 metabolized, 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 impairment:
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min) 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 tp 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 Cmax values were significantly increased by 200 % and 79 % respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic impairment:
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment (see section 4.2 Posology and method of administration). The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child Pugh class C) have 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate,
Film coat
hypromellose, titanium dioxide (E171), lactose monohydrate, glycerol triacetate, indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store below 30°C, in a dry place

6.4 Nature and contents of container

VIAGRA® Tablets 25 mg: Aclar / Aluminium foil blisters in cartons of 1, 4, 8 and 12.
VIAGRA® Tablets 50 mg: Aclar / Aluminium foil blisters in cartons of 1, 4, 8 and 12.
VIAGRA® Tablets 100 mg: Aclar / Aluminium foil blisters in cartons of 1, 4, 8 and 12.

6.5 Special precautions for disposal

No special instructions are required.

Manufacturer: : FAREVA AMBOISE Poce-Sure Cisse, France

License holder : Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725