Country: Israel

VIAGRA™ Tablets –
Combined 25 mg, 50 mg, 100 mg version. 23.12.2007

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIAGRA™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIAGRA 25 mg: Each tablet contains sildenafil citrate equivalent to 25 mg sildenafil.
VIAGRA 50 mg: Each tablet contains sildenafil citrate equivalent to 50 mg sildenafil.
VIAGRA 100 mg: Each tablet contains sildenafil citrate equivalent to 100 mg sildenafil.
For 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.

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 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 Fforms of interaction**.

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

Use in the elderly
In elderly patients above the age of 65 there may be an increase in plasma levels of up to 40%. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Use in children
Sildenafil is not indicated for use in children.

4.3 Contraindications

Use of sildenafil is contraindicated in patients with a known hypersensitivity to any component of the tablet.
Consistent with its known effects on the nitric oxide/c GMP pathway (see 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 Interaction with Other Medicinal products and Other Forms of Interaction).

4.4 Special warnings and special 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.

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).

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, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage and transient ischemic attack 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). 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). There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered with caution to 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.

Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see POST-MARKETING EXPERIENCE/Special Senses).

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.

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). However, there was no increased incidence of adverse events in these patients.
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

dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics

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 . Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

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.

Population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin), 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 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.

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).

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. (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.

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.

No interaction was seen when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additional reduction on supine blood pressure (systolic, 8 mmHg; diastolic, 7 mmHg) was of a similar magnitude to that seen when sildenafil was administered alone to healthy volunteers (see Pharmacodynamic properties).

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 Pregnancy and lactation

Sildenafil is not indicated for use in 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

4.8 Undesirable effects

Sildenafil was administered to over 3700 patients (aged 19-87) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

Treatment with sildenafil was well tolerated. In placebo controlled clinical studies, the discontinuation rate due to adverse events was low and similar to placebo. The adverse events were generally transient and mild to moderate in nature.
Across trials of all designs, the profile of adverse events reported by patients receiving sildenafilwas similar. In fixed dose studies, the incidence of 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 following adverse events were reported > 1% and < 5% by patients treated with sildenafil in PRN flexible-dose phase II/III studies and are considered clinically important and/or possibly related to drug treatment:

Body As A Whole: asthenia, pain, abdominal pain, back pain, infection, flu syndrome

Cardiovascular: headache*, flushing*, palpitation, vasodilatation*

Digestive: dyspepsia*, diarrhea, nausea

Musculoskeletal: arthralgia, myalgia

Nervous: dizziness*, hypertonia, insomnia

Respiratory: nasal congestion, pharyngitis, rhinitis*, sinusitis, respiratory tract infection, respiratory disorder

Skin and Appendages: rash

Special Senses: abnormal vision* (mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision), conjunctivitis

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc

ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see **Special warnings and special precautions for use**).

Urogenital: urinary tract infection, prostatic disorder

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.

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

*Treatment related clinical trial event

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.

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: ATC Code G04B E03 (proposed)

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. 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. 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.

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.

Its effect is more potent on PDE5 than on other known phosphdiesterases (10 fold for PDE6, >80-fold selectivity for PDE1, >700-fold for PDE2, PDE3, and PDE4, PDE7-PDE11).

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).

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

5.1.1 Further information on clinical trials

The efficacy and safety of sildenafil was evaluated in 21 randomised, 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 aetiologies (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 function, 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).

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 after oral administration, with mean absolute bioavailability of 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 Tmax of 60 minutes and a mean reduction in Cmax of 29%, however, the extent of absorption was not significantly affected (AUC decreased by 11%).

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.

Metabolism
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 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 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 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 (85%) 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

Sildenafil shows no evidence of any mutagenic or carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide (E171), lactose, triacetin, indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store below 30^{o}C.

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: Pfizer 37530 Poce-Sure Cisse, France

For: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725