SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

VIAGRA® 25 mg Tablets

VIAGRA® 50 mg Tablets

VIAGRA® 100 mg Tablets

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.

VIAGRA film-coated tablets contain the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, triacetin, indigo carmine aluminium lake.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.5 Vasodilators – peripheral

PHARMACOLOGICAL ACTION:

Sildenafil restores impaired erectile function by increasing blood flow to the penis, in response to sexual stimulation.

Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, during sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum allowing the inflow of blood.

Pharmacokinetic properties:

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 approximately 40 % (range 25 – 63 %). The oral pharmacokinetics of sildenafil is proportional over the recommended dose range (25 – 100 mg).

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 %.

Distribution:

The mean steady state volume of distribution (V_{ss}) 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.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0,0002 % (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Metabolism:

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50 % that of the parent drug. Plasma concentrations of this metabolite are approximately 40 % of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 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 faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

Pharmacokinetics in special patient groups:

Elderly:

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40 % greater than those seen in healthy younger volunteers (18 – 45 years).

Renal insufficiency:

In volunteers with mild (CLcr (creatinine clearance) = 50 – 80 ml/min) and moderate (CLcr = 30 – 49 ml/min) renal impairment, the pharmacokinetics of a single oral dose of VIAGRA (50 mg) were not altered. In volunteers with severe (CLcr ≤ 30 ml/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100 %) and C_{max} (88 %) compared to age-matched volunteers with no renal impairment.

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.

Pre-clinical safety data:

Sildenafil shows no evidence of any mutagenic or carcinogenic potential.

INDICATIONS:

VIAGRA is indicated only for the treatment of erectile dysfunction.

THIS PRODUCT IS NOT AN APHRODISIAC.

CONTRAINDICATIONS:

Use of VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet.

Consistent with its known effects on the nitric oxide/cGMP pathway (see PHARMACOLOGICAL ACTION), VIAGRA 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. Doctors should discuss with patients the contraindication of VIAGRA with concurrent organic nitrates.

Concomitant use of VIAGRA with potent cytochrome P450 3A4 inhibitors e.g. ritonavir, erythromycin, saquinavir, ketoconazole and itraconazole is contraindicated.

The use of VIAGRA is contraindicated in patients with severe hepatic impairment and patients

with severe impairment of renal function (creatinine clearance < 30 ml/min) not on haemodialysis or continuous ambulatory peritoneal dialysis.

WARNINGS AND SPECIAL PRECAUTIONS:

There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

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

VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers. Physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely 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 VIAGRA in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening dysrhythmia 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;
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. 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.

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.

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

Concomitant administration of VIAGRA to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see INTERACTIONS). In order to minimize the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating VIAGRA treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.

VIAGRA has no effect on bleeding time, including during co-administration with aspirin. *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 VIAGRA to patients with bleeding disorders or active peptic ulceration. Therefore, VIAGRA should be administered with caution to these patients.

Non-arteritic anterior ischaemic optic neuropathy (NAION) with some loss of vision or irreversible blindness has been reported with the use of selective phosphodiesterase type inhibitors including VIAGRA. NAION appears to be a class effect of these medicines.

Most of these patients had risk factors such as low cup to disc ratio ("crowded disk"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking.

A sudden unilateral or bilateral decrease or loss of hearing (sensorineural deafness) with or without associated vestibular symptoms has been reported with the use of PDE5 inhibitors, including VIAGRA. There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

The film coating of the VIAGRA tablet contains lactose. VIAGRA should not be administered to men

with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines:

As dizziness and altered vision were reported in clinical trials with VIAGRA, patients should be aware how they react to VIAGRA and exercise caution before driving, operating hazardous machinery or performing hazardous tasks.

INTERACTIONS:

Effects of other medicines on VIAGRA:

In vitro studies:

VIAGRA metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce VIAGRA clearance.

In vivo studies:

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

Population pharmacokinetic analysis of clinical trial data indicated a reduction in VIAGRA clearance when co-administered with CYP3A4 inhibitors (such as itraconazole, ketoconazole, erythromycin, and cimetidine). However, there was no increased incidence of adverse events in these patients.

When a single 100 mg dose of VIAGRA was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg two times daily for 5 days), there was a 182 % increase in VIAGRA systemic exposure (AUC).

In addition, co-administration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1 200 mg three times daily) with VIAGRA (100 mg single dose) resulted in a 140 % increase in VIAGRA C_{max} and a 210 % increase in VIAGRA AUC. VIAGRA had no effect on saquinavir pharmacokinetics (see DOSAGE AND DIRECTIONS FOR USE). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have still 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 VIAGRA (100 mg single dose) resulted in a 300 % (4-fold)

increase in VIAGRA C_{max} and a 1 000 % (11-fold) increase in VIAGRA plasma AUC. At 24 hours, the plasma levels of VIAGRA were still approximately 200 ng/ml, compared to approximately 5 ng/ml when VIAGRA was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. VIAGRA had no effect on ritonavir pharmacokinetics (see DOSAGE AND DIRECTIONS FOR USE).

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of VIAGRA.

Population pharmacokinetic analysis showed no effect of concomitant medication on VIAGRA 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, C_{max}, T_{max} elimination rate constant, or subsequent half-life of VIAGRA or its major circulating metabolite.

Effects of VIAGRA on other medicines:

In vitro studies:

VIAGRA is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 µM). Given VIAGRA peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

In vivo studies:

VIAGRA 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 VIAGRA is contraindicated (see CONTRAINDICATIONS).

In three specific drug-drug interactions studies, the alpha-blocker doxazosin (4 mg and 8 mg) and VIAGRA (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 VIAGRA and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope. Concomitant administration of VIAGRA to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see WARNINGS AND SPECIAL PRECAUTIONS).

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

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

VIAGRA (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dL.

Analysis of the safety database showed no difference in the side effect profile in patients taking VIAGRA with and without anti-hypertensive medication.

PREGNANCY AND LACTATION:

VIAGRA 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 VIAGRA.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

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

DOSAGE AND DIRECTIONS FOR USE:

VIAGRA 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.

The following factors are associated with increased plasma levels of VIAGRA:

Age > 65 (40 % increase in AUC), hepatic impairment (e.g. cirrhosis, 80 %), severe renal impairment (creatinine clearance < 30 ml/min, 100 %), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin 182 %, saquinavir 210 %, ketoconazole, itraconazole, 200 %, ritonavir 1000 %).

Use in patients with mild to moderately impaired renal function:

A starting dose of 25 mg should not be exceeded.

Use in patients with mild to moderately impaired hepatic function:

Since VIAGRA clearance is reduced in patients with hepatic impairment (e.g. cirrhosis), a starting dose of 25 mg should not be exceeded.

Use in elderly patients:

Healthy elderly volunteers (65 years or over) had a reduced clearance of VIAGRA. A starting dose of 25 mg should be considered in patients older than 65 years of age.

Use in patients using potent CYP 3A4 inhibitors:

Given the extent of the interaction with patients receiving concomitant therapy with cytochrome P450 3A4 inhibitors (e.g. ritonavir, erythromycin, saquinavir, ketoconazole, itraconazole), VIAGRA should not be used concomitantly with these agents (see CONTRAINDICATIONS).

VIAGRA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

Use in children:

VIAGRA is not indicated for use in children.

SIDE EFFECTS:

The side effects reported in clinical trials were categorized utilizing the incidence rate as follows:

Very common: ≥ 1/10

Common: ≥ 1/100 and < 1/10

Uncommon: ≥ 1/1 000 and < 1/100

Rare: ≥ 1/10 000 and < 1/1 000

Very rare:< 1/10 000

System Organ Class	**Frequency**	**The following adverse events occurred in ≥ 1 % patients in controlled clinical trials and may be considered to be treatment related**	**The following adverse events occurred in patients in controlled clinical trials, however a causal relationship to VIAGRA is uncertain**
Infections and infestations	Common		Flu syndrome
	Uncommon		Respiratory tract infection, infection, Herpes simplex, pharyngitis, bronchitis
	Rare		Sinusitis, urinary tract infection, laryngitis
Blood and lymphatic system disorders	Uncommon		Anaemia
	Rare		Leukopenia
Immune system disorders	Rare		Allergic reaction
Metabolic and nutrition disorders	Uncommon		Unstable diabetes
	Rare		Hyperglycaemia, hypernatraemia, gout, hyperuricaemia, hypoglycaemic reaction
Psychiatric disorders	Uncommon		Insomnia
	Rare		Depression, abnormal dreams, anorgasmia
Nervous system	Very common	Headache	

disorders	Common	Dizziness	
	Uncommon		Hypertonia, paraesthesia, somnolence, hypoaesthesia, ataxia, neuropathy
	Rare		Vertigo, migraine, myasthenia, tremor, reflexes decreased, neuralgia
Eye disorders	Common	Abnormal vision (increased perception of light, blurred vision), chromatopsia (mild and transient, predominantly colour tinge to vision)	
	Uncommon		Conjunctivitis, photophobia
	Rare		Dry eyes, eye haemorrhage, eye pain, cataract
Ear and labyrinth disorders	Uncommon		Tinnitus
	Rare		Deafness, ear pain
Cardiac disorders	Common	Palpitations	
	Uncommon		Tachycardia, angina pectoris
	Rare		AV block, cardiac arrest, heart failure, cardiomyopathy
Vascular disorders	Very common	Vasodilatation (flushing)	
	Rare		Hypotension, epistaxis, shock, postural hypotension
Respiratory, thoracic and mediastinal	Common	Rhinitis (nasal congestion)	
	Uncommon		Respiratory disorder, dyspnoea, asthma

disorders	Rare		Increased cough, increased sputum
Gastrointestinal disorders	Common	Dyspepsia	
	Uncommon		Dry mouth, diarrhoea, nausea, vomiting, abdominal pain, gastritis, gastroenteritis, gingivitis, rectal haemorrhage
	Rare		Glossitis, oesophagitis, colitis, dysphagia, stomatitis
Skin and subcutaneous tissue disorders	Uncommon		Sweating, rash, skin ulcer
	Rare		Pruritus, face oedema, exfoliative dermatitis, photosensitivity reaction, urticaria, contact dermatitis
Musculoskeletal and connective tissue disorders	Uncommon		Arthralgia, myalgia, back pain, tenosynovitis, synovitis
	Rare		Arthritis, tendon rupture, arthrosis, bone pain
Renal and urinary disorders	Rare		Cystitis, nocturia, urinary frequency/incontinence, haematuria
Reproductive system and breast disorders	Rare		Abnormal ejaculation, prostatic disorder, breast enlargement, genital oedema
General disorders and administration site conditions	Uncommon		Asthenia, pain, chest pain, thirst
	Rare		Chills, oedema, peripheral

			oedema
Investigations	Rare		Abnormal electrocardiogram, liver function tests abnormal
Injury poisoning and procedural complications	Uncommon		Accidental injury/fall

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

Other events that have been reported in post-marketing surveillance and not listed in the pre-marketing experience include:

System Organ Class	**Adverse event**
Immune system disorders	Hypersensitivity reactions (including skin rashes)
Nervous system disorders	Seizure, seizure recurrence
Eye disorders	Red eyes/bloodshot eyes, non-arteritic anterior ischaemic optic neuropathy with some loss of vision or irreversible blindness, diplopia, temporary vision loss/decreased vision, ocular burning, ocular swelling/pressure, increased intra-ocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular oedema
Cardiac disorders	Myocardial infarction, sudden cardiac death, ventricular dysrhythmia
Vascular disorders	Hypotensive events after the use of VIAGRA in combination with alpha blockers, syncope, cerebrovascular haemorrhage, transient ischaemic attack, hypertension
Reproductive system and breast disorders	Prolonged erection, priapism

Health care professionals are encouraged to report any unexpected and/or serious adverse events associated with the use of VIAGRA to: Pfizer Laboratories at 0860 PFIZER (734 937), or The Medicines Control Council National Adverse Drug Event Monitoring Center at (021) 447

1618.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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, supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as VIAGRA is highly bound to plasma proteins and not eliminated in the urine.

IDENTIFICATION:

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

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

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

PRESENTATION:

VIAGRA 25 mg, 50 mg, 100 mg: Aluminium foil/clear PVC blisters are packed into a white printed outer cardboard carton with a package insert. The film-coated tablets are available in pack sizes of 1, 2, 4, 8 and 12.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of the reach of children.

REGISTRATION NUMBERS:

VIAGRA 25 mg: 32/7.1.5/0621

VIAGRA 50 mg: 32/7.1.5/0622

VIAGRA 100 mg: 32/7.1.5/0623

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

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South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

02 March 2012

BOTSWANA: S2

VIAGRA 25 mg – Reg. No.: BOT9900339

VIAGRA 50 mg – Reg. No.: BOT9900340

VIAGRA 100 mg – Reg. No.: BOT9900341

NAMIBIA: NS2

VIAGRA 25 mg – Reg. No.: 2001/A7.1/005

VIAGRA 50 mg – Reg. No.: 2001/A7.1/003

VIAGRA 100 mg – Reg. No.: 2001/A7.1/004

ZAMBIA: POM

VIAGRA 50 mg – Reg. No.:120/003

ZIMBABWE: PP

VIAGRA 50 mg – Reg. No.: 2000/21.8/3778

VIAGRA 100 mg – Reg. No.: 2000/21.8/3779