SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

AVIGRA® 25 Film-coated tablets

AVIGRA® 50 Film-coated tablets

AVIGRA® 100 Film-coated tablets

COMPOSITION:

AVIGRA 25: Each film-coated tablet contains sildenafil citrate equivalent to 25 mg sildenafil.

AVIGRA 50: Each film-coated tablet contains sildenafil citrate equivalent to 50 mg sildenafil.

AVIGRA 100: Each film-coated tablet contains sildenafil citrate equivalent to 100 mg sildenafil.

AVIGRA 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:

Pharmacodynamics:

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 nitric oxide on this tissue. When the nitric oxide/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.

Pharmacokinetics:

Absorption:

Sildenafil is well 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 sildenafil 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 substance. 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 (CL_{CR} = 50 – 80 ml/min) and moderate (CL_{CR} = 30 – 49 ml/min) renal

impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe ($CL_{CR} \leq 30$ 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 (see DOSAGE AND DIRECTIONS FOR USE).

Hepatic insufficiency:

In volunteers with hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84 %) and C_{max} (47 %) compared to age-matched volunteers with no hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE).

INDICATIONS:

AVIGRA is indicated for the treatment of erectile dysfunction.

AVIGRA IS NOT AN APHRODISIAC.

CONTRAINDICATIONS:

Use of AVIGRA is contraindicated in patients with a known hypersensitivity to any component of the film-coated tablet.

Consistent with its known effects on the nitric oxide/cGMP pathway (see PHARMACOLOGICAL ACTION), AVIGRA 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 AVIGRA with concurrent organic nitrates.

Concomitant use of AVIGRA with potent cytochrome P450 3A4 inhibitors e.g. ritonavir, erythromycin, saquinavir, ketoconazole and itraconazole is contraindicated (see INTERACTIONS).

The use of AVIGRA 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 adverse effects during sexual activity in patients with pre-existing cardiovascular disease. Therefore, AVIGRA 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.

AVIGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers. Medical practitioners 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 are no controlled clinical data on the safety or efficacy of AVIGRA in the following patient 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 mmHg) or hypertension (BP > 170/110 mmHg);
- Patients with cardiac failure or coronary artery disease causing unstable angina;
- Patients with retinitis pigmentosa (these patients may have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) may occur. 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.

AVIGRA should not be used 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).

AVIGRA should not be used in men for whom sexual activity is inadvisable.

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

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

There is no safety information on the administration of AVIGRA to patients with bleeding disorders or active peptic ulceration. Therefore, AVIGRA should be administered with caution to these patients.

Non arteritic anterior ischaemic optic neuropathy (NAION) with loss of vision or irreversible blindness has been reported with the use of selective phosphodiesterase type inhibitors including AVIGRA. 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 AVIGRA. 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 AVIGRA tablet contains lactose. AVIGRA 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 AVIGRA, patients should be aware how they react to AVIGRA and exercise caution before driving, operating hazardous machinery or performing hazardous tasks.

INTERACTIONS:

Effects of other medicines on AVIGRA:

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.

In vivo studies:

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

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil 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.

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

When a single 100 mg dose of AVIGRA 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 AVIGRA systemic exposure (AUC).

The HIV protease inhibitors such as saquinavir, also a CYP3A4 inhibitor, may reduce clearance of AVIGRA. Co-administration of saquinavir at steady state (1 200 mg three times daily) with AVIGRA (100 mg single dose) resulted in a 140 % increase in AVIGRA C_{max} and a 210 % increase in AVIGRA AUC. AVIGRA 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.

HIV protease inhibitor, ritonavir increases plasma concentration of AVIGRA significantly and such combinations should not be given unless absolutely essential. Co-administration of ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with AVIGRA (100 mg single dose) resulted in a 300 % (4-fold) increase in AVIGRA C_{max} and a 1 000 % (11-fold) increase in AVIGRA plasma AUC. At 24 hours, the plasma levels of AVIGRA were still approximately 200 ng/ml, compared to approximately 5 ng/ml when AVIGRA was dosed alone. AVIGRA had no effect on ritonavir pharmacokinetics (see DOSAGE AND DIRECTIONS FOR USE).

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, 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 AVIGRA or its major circulating metabolite.

Effects of AVIGRA on other medicines:

In vitro studies:

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 > 150 micromolar). Given sildenafil peak plasma concentrations of approximately 1 micromolar after recommended doses, it is unlikely that AVIGRA will alter the clearance of substrates of these isoenzymes. *In vitro* studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor) (see CONTRAINDICATIONS).

In vivo studies:

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

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

AVIGRA 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 AVIGRA is contraindicated (see CONTRAINDICATIONS).

In three specific interactions studies, the alpha-blocker doxazosin (4 mg and 8 mg) and AVIGRA (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilised on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When AVIGRA and doxazosin were administered simultaneously to patients stabilised on doxazosin therapy, there were reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light headedness, but not syncope. Concomitant administration of

AVIGRA to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals (see WARNINGS AND SPECIAL PRECAUTIONS).

PREGNANCY AND LACTATION:

AVIGRA is not indicated for use in women.

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

DOSAGE AND DIRECTIONS FOR USE:

AVIGRA film-coated 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 sildenafil:

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 1 000 %) (see CONTRAINDICATIONS).

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 AVIGRA 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 AVIGRA. 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), AVIGRA should not be used concomitantly with these agents (see CONTRA-INDICATIONS).

AVIGRA 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:

AVIGRA is not indicated for use in children.

SIDE EFFECTS:

Infections and infestations:

Frequent: Flu syndrome.

Less frequent: Respiratory tract infection, infection, urinary tract infection.

Blood and lymphatic system disorders:

Less frequent: Anaemia.

Frequency unknown: Leucopenia.

Immune system disorders:

Less frequent: Facial oedema, shock, allergic reaction.

Metabolism and nutrition disorders:

Less frequent: Thirst, gout, unstable diabetes, hypoglycaemic reaction, hyperglycaemia, hypernatraemia.

Nervous system disorders:

Less frequent: Asthenia, ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypoaesthesia, headache, migraine, dizziness.

Frequency unknown: Accidental fall, accidental injury.

Eye disorders:

Less frequent: Abnormal vision, chromatopsia (predominantly colour tinge to vision), but also increased perception of light or blurred vision. Conjunctivitis, eye haemorrhage, eye pain, cataract, dry eyes.

Frequency unknown: Photophobia.

Ear and labyrinth disorders:

Less frequent: Tinnitus, deafness, ear pain.

Cardiac disorders:

Serious cardiovascular events have been reported. Most, but not all, of these patients had pre-existing cardiovascular risk factors.

Less frequent: Angina pectoris, AV block, tachycardia, palpitations, cardiac arrest, heart failure.

Frequency unknown: Abnormal electrocardiogram. Cardiomyopathy has been reported (see WARNINGS AND SPECIAL PRECAUTIONS).

Vascular disorders:

Less frequent: Epistaxis, hypotension, postural hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Rhinitis (nasal congestion).

Less frequent: Asthma, dyspnoea, laryngitis, pharyngitis, sinusitis, bronchitis, increased sputum, increased coughing, respiratory disorder.

Gastrointestinal disorders:

Frequent: Dyspepsia.

Less frequent: Abdominal pain, vomiting, diarrhoea, nausea, glossitis, colitis, dysphagia, gastritis, gastroenteritis, oesophagitis, stomatitis, dry mouth, rectal haemorrhage, gingivitis.

Hepatobiliary disorders:

Frequency unknown: Abnormal liver function tests.

Skin and subcutaneous tissue disorders:

Frequent: Vasodilatation (flushing).

Less frequent: Urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis, photosensitivity reaction, erythema, rash.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthritis, arthrosis, myalgia, tendon rupture (bone pain), tenosynovitis, myasthenia, synovitis, myalgia, arthralgia, back pain.

Renal and urinary disorders:

Less frequent: Cystitis, nocturia, urinary frequency, urinary incontinence, hyperuricaemia, haematuria.

Reproductive system and breast disorders:

Less frequent: Breast enlargement, abnormal ejaculation, anorgasmia, prostatic disorder.

Frequency unknown: Genital oedema.

General disorders and administrative site conditions:

Less frequent: Fever, pain, chest pain, chills, oedema, peripheral oedema.

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 for sildenafil and not listed in the pre-marketing experience include:

System Organ Class	**Adverse event**
Immune system disorders	Hypersensitivity reactions (including skin rashes), paramacular oedema
Nervous system disorders	Seizure, seizure recurrence, syncope
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
Cardiac disorders	Myocardial infarction, sudden cardiac death, ventricular dysrhythmia, transient ischaemic attack, hypertension
Vascular disorders	Hypotensive events after the use of AVIGRA in combination with alpha blockers, cerebrovascular haemorrhage
Reproductive system and breast disorders	Prolonged erection, priapism

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 were increased.

In cases of overdose, 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.

IDENTIFICATION:

AVIGRA 25: Blue, rounded diamond shaped film-coated tablets (9,2 x 6,7 mm approximate dimensions) debossed with “VGR 25” on one side and “Pfizer” on the other.

AVIGRA 50: Blue, rounded diamond shaped film-coated tablets (11,2 x 8,1 mm approximate dimensions) debossed with “VGR 50” on one side and “Pfizer” on the other.

AVIGRA 100: Blue, rounded diamond shaped film-coated tablets (14,1 x 10,2 mm approximate dimensions) debossed with “VGR 100” on one side and “Pfizer” on the other.

PRESENTATION:

AVIGRA 25, 50, 100: 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. Store the blisters in the carton until required for use. Keep out of the reach of children.

REGISTRATION NUMBERS:

AVIGRA 25: 43/7.1.5/0886

AVIGRA 50: 43/7.1.5/0887

AVIGRA 100: 43/7.1.5/0888

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

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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BOTSWANA: S2

AVIGRA 25: Reg. No.: BOT1302494

AVIGRA 50: Reg. No.: BOT1302495

AVIGRA 100: Reg. No.: BOT1302496

NAMIBIA: NS2

AVIGRA 25: Reg. No.: 13/7.1.5/0082

AVIGRA 50: Reg. No.: 13/7.1.5/0083

AVIGRA 100: Reg. No.: 13/7.1.5/0084

ZIMBABWE: PP

AVIGRA 25: Reg. No.: 2014/31/4872

AVIGRA 50: Reg. No.: 2014/31/4871

AVIGRA 100: Reg. No.: 2014/31/4870