SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

AVIGRA® 25 film-coated tablets

AVIGRA® 50 film-coated tablets

AVIGRA® 100 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE 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.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each AVIGRA 25 film-coated tablet contains 0,919 mg lactose monohydrate.

Each AVIGRA 50 film-coated tablet contains 1,837 mg lactose monohydrate.

Each AVIGRA 100 film-coated tablet contains 3,675 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

AVIGRA 25: Blue, rounded-diamond shaped film-coated tablets debossed with “VGR 25” on one side and “Pfizer” on the other.

AVIGRA 50: Blue, rounded-diamond shaped film-coated tablets debossed with “VGR 50” on one side and “Pfizer” on the other.

AVIGRA 100: Blue, rounded-diamond shaped film-coated tablets debossed with “VGR 100” on one side and “Pfizer” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVIGRA is indicated only for the treatment of erectile dysfunction.

AVIGRA IS NOT AN APHRODISIAC.

4.2 Posology and method of administration

Posology

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 AVIGRA

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 section 4.3).

Special populations

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 medicines (see section 4.3).

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 (see section 4.3).

Paediatric population

AVIGRA is not indicated for use in children below 18 years of age.

Method of administration

AVIGRA tablets are for oral use.

4.3 Contraindications

Use of AVIGRA is contraindicated in patients with a known hypersensitivity to sildenafil or to any excipients of AVIGRA (listed in section 6.1).

Administration of AVIGRA to patients who are using nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently is contraindicated.

Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), AVIGRA was shown to potentiate the hypotensive effects of acute and chronic nitrates. Medical practitioners should discuss with patients the contraindication of concurrent use of AVIGRA with organic nitrates.

Concomitant use of AVIGRA with potent cytochrome P450 3A4 inhibitors e.g. ritonavir, erythromycin, saquinavir, ketoconazole and itraconazole is contraindicated (see section 4.5).

AVIGRA 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.

The co-administration of PDE5 inhibitors, including AVIGRA, with guanylate cyclase stimulators such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

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.

4.4 Special warnings and precautions for use

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular dysrhythmia, cerebrovascular haemorrhage and transient ischaemic attack have

been reported post-marketing in temporal association with the use of AVIGRA 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 AVIGRA without sexual activity. Others were reported to have occurred hours to days after the use of AVIGRA and sexual activity. It is not possible to determine whether these events are related directly to AVIGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors. **The cardiovascular status of patients should be assessed prior to initiating treatment for erectile dysfunction.** AVIGRA should not be used in men for whom sexual activity is inadvisable.

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

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.

Non-arteritic anterior ischaemic optic neuropathy (NAION) with some loss of vision or irreversible blindness has been reported with the use of PDE5 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.

In case of sudden visual loss, patients should be advised to stop taking AVIGRA and consult a medical practitioner immediately.

Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, medical practitioners should discuss this risk with these patients and whether they could be adversely affected by use of PDE5 inhibitors. PDE5 inhibitors, including AVIGRA, should be used with caution in these patients and the patient's NAION risk factors should be evaluated when considering prescribing AVIGRA.

NAION appears to be a class effect of these medicines.

Concomitant administration of AVIGRA to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals (see section 4.5). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating AVIGRA treatment. Initiation of AVIGRA at lower doses should be considered (see section 4.2). Medical practitioners should advise patients what to do in the event of postural hypotensive symptoms.

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.

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 AVIGRA to patients with retinitis pigmentosa, therefore, AVIGRA should be administered with caution to these patients.

AVIGRA 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 AVIGRA to patients with bleeding disorders or active peptic ulceration. Therefore, AVIGRA should be administered with caution to these patients.

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).

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

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. In case of sudden decrease or loss of hearing, patients should be advised to stop taking AVIGRA and consult a medical practitioner promptly.

The film-coating of the AVIGRA tablet contains lactose. Men with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on AVIGRA

In vitro studies:

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

In vivo studies:

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

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 AVIGRA (50 mg) to healthy volunteers.

When a single 100 mg dose of AVIGRA was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg two times daily for 5 days), there was a 182 % increase in AVIGRA 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 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 section 4.2). 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 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. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. AVIGRA had no effect on ritonavir pharmacokinetics (see section 4.2).

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

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 AVIGRA at steady state (80 mg three times a day) resulted in 62,6 % and 55,4 % decrease in AVIGRA AUC and C_{max}, respectively. AVIGRA increased bosentan AUC and C_{max} by 49,8 % and 42 %, respectively. Concomitant administration of strong CYP3A4 inducers, such as rifampicin, is expected to cause greater decreases in plasma concentrations of AVIGRA.

Pharmacokinetic data from patients in clinical trials showed no effect on AVIGRA pharmacokinetics of 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 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:

AVIGRA is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 µM).

Given AVIGRA peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that AVIGRA will alter the clearance of substrates of these isoenzymes.

In vivo studies:

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 section 4.3).

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 a few susceptible individuals (see section 4.4).

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

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

AVIGRA at steady state (80 mg three times a day) resulted in a 49,8 % increase in bosentan AUC and a 42 % increase in bosentan Cmax (125 mg twice a day) (see *Effects of other medicines on AVIGRA*).

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 4,4 mmol/L.

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

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

4.6 Fertility, 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.

4.7 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.

4.8 Undesirable effects

The most commonly reported adverse reactions were headache and flushing.

Tabulated summary of adverse reactions

The side effects reported in clinical trials were categorised utilising the incidence rate as follows: 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), very rare (< 1/10 000).

MedDRA system organ class	**Frequency**	**Side effects**
Infections and infestations	Common	Rhinitis, flu syndrome
	Uncommon	Respiratory tract infection, infection, herpes simplex, pharyngitis, bronchitis
	Rare	Urinary tract infection, sinusitis, laryngitis
Blood and lymphatic system disorders	Uncommon	Anaemia
	Rare	Leukopenia
Immune system disorders	Uncommon	Hypersensitivity reactions (including skin rashes)
	Rare	Allergic reaction

Metabolism and nutrition disorders	Uncommon	Unstable diabetes
	Rare	Hyperglycaemia, hypernatraemia, gout, hyperuricaemia, hypoglycaemic reaction
Psychiatric disorders	Uncommon	Insomnia
	Rare	Depression, abnormal dreams, anorgasmia
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence, hypertonia, paraesthesia, hypoaesthesia, ataxia, neuropathy
	Rare	Syncope, vertigo, migraine, myasthenia, tremor, decreased reflexes, neuralgia
Eye disorders	Common	Blurred vision, visual disturbance, cyanopsia, abnormal vision (increased perception of light), chromatopsia (mild and transient, predominantly colour tinge to vision)
	Uncommon	Eye pain, photophobia, photopsia, ocular hyperaemia, visual brightness, conjunctivitis
	Rare	Eye oedema, eye swelling, dry eye, asthenopia, halo vision, xanthopsia, erythropsia, eye disorder, conjunctival hyperaemia, eye irritation, abnormal sensation in eye, eyelid oedema, eye haemorrhage, 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	Vasodilation (flushing)

	Common	Hot flush
	Uncommon	Hypotension
	Rare	Shock, postural hypotension
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion
	Uncommon	Epistaxis, sinus congestion, respiratory disorder, dyspnoea, asthma
	Rare	Throat tightness, nasal dryness, nasal oedema, increased cough, increased sputum
Gastrointestinal disorders	Common	Nausea, dyspepsia
	Uncommon	Gastroesophageal reflux disease, vomiting, upper abdominal pain, dry mouth, diarrhoea, gastritis, gastroenteritis, gingivitis, rectal haemorrhage
	Rare	Oral hypoaesthesia, glossitis, oesophagitis, colitis, dysphagia, stomatitis
Skin and subcutaneous tissue disorders	Uncommon	Rash, sweating, skin ulcer
	Rare	Pruritus, face oedema, exfoliative dermatitis, photosensitivity reaction, urticaria, contact dermatitis, erythema
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia, pain in extremity, arthralgia, 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	Increased erection, abnormal ejaculation, prostatic disorder, breast enlargement, genital oedema
General disorders and administration site conditions	Uncommon	Feeling hot, asthenia, pain, chest pain, thirst
	Rare	Irritability, chills, oedema, peripheral oedema

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

Post-marketing experience

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

MedDRA system organ class	**Side effects**
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 AVIGRA in combination with alpha blockers, cerebrovascular haemorrhage, transient ischaemic attack, hypertension
Reproductive system and breast disorders	Prolonged erection, priapism

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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.

Side effects may be exacerbated or exaggerated (see section 4.8).

In cases of overdose, supportive measures should be adopted as required.

Renal dialysis is not expected to accelerate clearance as AVIGRA is highly bound to plasma proteins and not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.5 Vasodilators – peripheral

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Mechanism of action

Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum.

When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

5.2 Pharmacokinetic properties

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

It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil.

Absorption

Sildenafil is rapidly absorbed after oral administration. The mean absolute oral bioavailability is approximately 41 % (range 25 – 63 %). Maximum observed plasma concentrations are reached within

30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. 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. When sildenafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29 %, however, the extent of absorption was not significantly affected (AUC decreased by 11 %).

Distribution

The mean steady state volume of distribution (V_{ss}) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96 % bound to plasma proteins. Protein binding is independent of total medicine 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-demethylation of sildenafil and is itself further metabolised. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50 % that of the parent medicine. In healthy volunteers, plasma concentrations of this metabolite are approximately 40 % of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 hours.

Elimination

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3 – 5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

Special populations

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).

In addition, N-desmethyl metabolite AUC and C_{max} 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 C_{max} (47 %) compared to age-matched volunteers with no hepatic impairment (see section 4.2). The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh class C) have not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate (anhydrous)

Croscarmellose sodium

Hypromellose

Indigo carmine aluminium lake

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Titanium dioxide

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Store the blisters in the carton until required for use.

6.5 Nature and contents of container

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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel.: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

AVIGRA 25: 43/7.1.5/0886

AVIGRA 50: 43/7.1.5/0887

AVIGRA 100: 43/7.1.5/0888

9. DATE OF FIRST AUTHORISATION

AVIGRA 25, 50, 100: 25 November 2011

10. DATE OF REVISION OF THE TEXT

22 February 2022

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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