PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RAVIAG 25 Film-coated tablets

RAVIAG 50 Film-coated tablets

RAVIAG 100 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

RAVIAG 25: Red coloured, rounded triangular shaped, film-coated tablets, with **'S21'** engraved on one side and plain on the other side.

RAVIAG 50: Red coloured, rounded triangular shaped, film-coated tablets, with **'S22'** engraved on one side and plain on the other side.

RAVIAG100: Red coloured, rounded triangular shaped, film-coated tablets, with **'S23'** engraved on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RAVIAG is indicated only for the treatment of erectile dysfunction.

THIS PRODUCT IS NOT AN APHRODISIAC.

4.2 Posology and method of administration

Posology

Use in adults

The recommended dose is 50 mg once a day as needed, taken one hour before sexual activity. Based on tolerance and efficacy, the dose may be increased to 100 mg or decreased to 25 mg. The maximum daily dose is 100 mg. The maximum dosing frequency is once per day.

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

Age > 65 (40 % increase in AUC), hepatic impairment (e.g. cirrhosis, 80 %), severe renal impairment (e.g. creatine clearance < 30 mL/min, 100 %), and concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin 182 %, saquinavir 210 %, ketoconazole, itraconazole, 200 %, ritonavir 1000 %, 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 RAVIAG 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 RAVIAG. 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 P4503A4 inhibitors (e.g. ritonavir, erythromycin, saquinavir, ketoconazole, itraconazole), RAVIAG should not be used concomitantly with these agents (see section 4.3).

RAVIAG 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.

Paediatric population

RAVIAG is not indicated for use in children.

Method of administration

RAVIAG tablets are for oral administration.

4.3 Contraindications

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

RAVIAG potentiates the hypotensive effects of acute and chronic nitrates (see section 4.5), and its co-administration with 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 RAVIAG with concurrent organic nitrates.

Concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, ritonavir, saquinavir, ketoconazole, itraconazole).

RAVIAG is also contraindicated in:

- **Severe hepatic impairment (e.g. cirrhosis).**
- **Severe renal impairment (e.g. creatinine clearance < 30 mL/min).**

4.4 Special warnings and precautions for use

There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including RAVIAG, should not be 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.

RAVIAG 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 (such as aortic stenosis or hypertrophic obstructive cardiomyopathy), or those with the syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

Concomitant administration of RAVIAG 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 RAVIAG treatment. Medical practitioners should advise patients what to do in the event of postural hypotensive symptoms.

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

The safety or efficacy of RAVIAG in the following patient groups have not been established; 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 (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. The patient should seek immediate medical assistance in the event of an erection that persists longer than 4 hours. Penile tissue damage and permanent loss of potency could result if

priapism is not treated immediately.

RAVIAG 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).

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

Interactions between RAVIAG and other antihypertensive medications have not been studied.

RAVIAG 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). Safety information on the administration of RAVIAG to patients with bleeding disorders or active peptic ulceration is not available. RAVIAG should therefore 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-5 inhibitors including sildenafil (contained in RAVIAG). 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. RAVIAG should not be given to these patients.

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 RAVIAG**.** There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

INFORMATION FOR PATIENTS

The use of RAVIAG offers no protection against sexually transmitted diseases. Counselling of patients about protective measures necessary to guard against sexually transmitted diseases, including the human immunodeficiency virus (HIV/AIDS) should be considered. Precautions against unwanted pregnancy should be taken.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on RAVIAG

In vitro studies:

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

In vivo studies:

Plasma sildenafil concentrations were increased by 56 % when cimetidine (800 mg), a non-specific CYP3A4 inhibitor, was co-administered with sildenafil (50 mg) to healthy volunteers.

Sildenafil clearance was reduced 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.

A 100 mg single dose of sildenafil co-administered with erythromycin 500 mg twice daily, resulted in a 182 % increase in sildenafil systemic exposure (AUC) at steady state.

Co-administration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1 200 mg three times daily) with RAVIAG (100 mg single dose) resulted in a 140 % increase in RAVIAG Cmax and a 210 % increase in RAVIAG AUC. RAVIAG 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 RAVIAG (100 mg single dose) resulted in a 300 % (4-fold) increase in RAVIAG C_{max} and a 1 000 % (11-fold) increase in RAVIAG plasma AUC. At 24 hours, the plasma levels of RAVIAG were still approximately 200 ng/ml, compared to approximately 5 ng/ml when RAVIAG was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. RAVIAG had no effect on ritonavir pharmacokinetics (see section 4.2).

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

Population pharmacokinetic analysis showed no effect of concomitant medication on RAVIAG 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 RAVIAG or its major circulating metabolite.

Effects of RAVIAG on other medicines

In vitro studies:

RAVIAG is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} >150 microM). Given RAVIAG peak plasma concentrations of approximately 1 microM after recommended doses, it is unlikely that sildenafil will alter the clearance of substrates of these isoenzymes.

In vivo studies:

RAVIAG was shown to potentiate the hypotensive effect of acute and chronic nitrates. Therefore, use of nitrates or nitric oxide donors with RAVIAG is contraindicated (see section 4.3).

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

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

RAVIAG (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 RAVIAG (100 mg) was co-administered with amlodipine in hypertensive patients.

No difference was seen in the side effect profile in patients taking RAVIAG with and without anti-hypertensive medication.

Symptomatic hypotension may occur when RAVIAG is administered concomitantly with alpha-blockers (see section 4.4).

4.6 Fertility, pregnancy and lactation

RAVIAG is not indicated for use in women.

Fertility

Reproduction studies in rats and rabbits showed no teratogenic effects, impairment of fertility or adverse effects on peri/postnatal development, following oral administration of sildenafil.

Single oral doses of 100 mg sildenafil in healthy volunteers did not have an effect on sperm motility or morphology.

4.7 Effects on ability to drive and use machines

As dizziness and altered vision may occur with RAVIAG, patients should be aware how they react to RAVIAG and exercise caution before driving, operating hazardous machinery or performing hazardous tasks.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Flu syndrome.
	Less frequent	Respiratory tract infection, infection, Herpes simplex, pharyngitis, bronchitis, sinusitis, urinary tract infection, laryngitis.
Blood and lymphatic system disorders	Less frequent	Anaemia and leukopenia.
Immune system disorders	Less frequent	Allergic reaction.
	Frequency not known	Hypersensitivity reactions (including skin rashes).
Metabolism and nutrition disorders	Less frequent	Gout, unstable diabetes, hyperglycaemia, hyperuricaemia, hypoglycaemic reaction,

		hypernatraemia.
Psychiatric disorders	Less frequent	Insomnia, depression, abnormal dreams, anorgasmia.
Nervous system disorders	Frequent	Headache, dizziness.
	Less frequent	Ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, vertigo, somnolence, decreased reflexes, migraine, myasthenia, tremor, hypoaesthesia.
	Frequency not known	Seizure, seizure recurrence.
Eye disorders	Frequent	Abnormal vision (increased perception of light, blurred vision), chromatopsia (mild and transient, predominantly colour tinge to vision).
	Less frequent	Conjunctivitis, photophobia, eye haemorrhage, cataract, dry eyes, eye pain.
	Frequency not known	Diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular oedema. Non-arteritic anterior ischaemic, optic neuropathy (NAION) causing permanent loss of vision.
Ear and labyrinth disorders	Less frequent	Tinnitus, ear pain, deafness.
Cardiac disorders	Frequent	Palpitation.
	Less frequent	Angina pectoris, AV block, tachycardia, cardiac arrest, heart failure, cardiomyopathy.

	Frequency not known	Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular dysrhythmia (see section 4.4).
Vascular disorders	Frequent	Flushing.
	Less frequent	Hypotension, epistaxis, shock, postural hypotension.
	Frequency not known	Hypotensive events after the use of RAVIAG in combination with alpha blockers, syncope, cerebrovascular haemorrhage, transient ischaemic attack and hypertension (see section 4.4**)**.
Respiratory, thoracic and mediastinal disorders	Frequent	Rhinitis (nasal congestion).
	Less frequent	Asthma, dyspnoea, respiratory disorder, increased sputum, increased cough.
Gastrointestinal disorders	Frequent	Dyspepsia.
	Less frequent	Vomiting, nausea, glossitis, colitis, dysphagia, gastritis, gastroenteritis, abdominal pain, oesophagitis, stomatitis, dry mouth, rectal haemorrhage, gingivitis, diarrhoea.
Skin and subcutaneous tissue disorders	Less frequent	Urticaria, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis, face oedema, photosensitivity reaction, rash, alopecia, cellulitis.
Musculoskeletal, and connective tissue disorders	Less frequent	Arthritis, arthrosis, arthralgia, myalgia, tendon rupture, and tenosynovitis, bone pain, synovitis, limb and/or back pain.
Renal and urinary disorders	Less frequent	Cystitis, nocturia, urinary frequency, urinary incontinence and haematuria.
Reproductive system and breast disorders	Less frequent	Abnormal ejaculation, prostatic disorder, genital oedema, breast enlargement.

	Frequency not known	Prolonged erection, priapism.
General disorders and administration site conditions	Less frequent	Asthenia, photosensitivity reaction, shock, pain, thirst, chills, oedema, peripheral oedema, chest pain.
Investigations	Less frequent	Abnormal electrocardiogram, abnormal liver function tests.
Injury, poisoning and procedural complications	Less frequent	Accidental injury/fall.

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 overdose, side effects can be precipitated and/or be of increased severity, see section 4.8.

In cases of overdose, treatment is symptomatic and supportive.

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

A 7.1.5 Vasodilators – peripheral

Sildenafil is a selective inhibitor of phosphodiesterase type 5 (PDE5), an enzyme responsible for degrading cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. By diminishing the effect of PDE5, sildenafil facilitates the effect of nitric oxide during sexual stimulation resulting in increased levels of cGMP,

smooth muscle relaxation, and allowing the inflow of blood into the corpus cavernosum, producing an erection.

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

5.2 Pharmacokinetic properties

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

A high fat meal reduces the rate of absorption with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29 %.

Distribution

The mean steady state volume of distribution (Vss) for sildenafil is 105 litres, 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.

Less than 0,0002 % of sildenafil remained in the semen of healthy volunteers 90 minutes after dosing.

Biotransformation

Sildenafil is metabolised by the CYP3A4 (major route) and CYP2C9 (minor route) via hepatic microsomal isoenzymes. Sildenafil is converted by N-demethylation to an active metabolite with properties similar to those of the parent compound sildenafil, and an *in vitro* potency for PDE5 approximately 50 % that of the parent compound. 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

After oral administration, sildenafil is excreted as metabolites mainly in the faeces (approximately 80 %) and to a lesser extent in the urine (approximately 13 %).

The total body clearance of sildenafil is 4 L/h with a resultant terminal phase half-life of 3 – 5 hours.

Special populations

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 = 50 – 80 mL/min) and moderate (CLcr = 30 – 49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium hydrogen phosphate

Cellulose microcrystalline

Croscarmellose sodium

Magnesium stearate

Film-coat

Aluminium lake

Hypromellose

Indigo carmine

Iron oxide red

Polyethylene glycol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C, in the original pack.

The blisters should be kept in the carton until required for use.

6.5 Nature and contents of container

The RAVIAG tablets are packed in PVC/PE/PVdC blister pack (triplex blister pack), transparent PVC blister pack and cold form blister pack.

Transparent PVC blister pack:

Clear PVC film with hard tempered, heat-sealable aluminium foil coated with heat seal lacquer on the inner side of the foil – should be odourless.

PVC/PE/PVdC blister pack (triplex blister pack):

The pack comprises of clear transparent PVC film, laminated with polyethylene (PE) and coated with PVdC on the inner side, with a backing of hard tempered heat-sealable aluminium foil coated with heat seal lacquer.

Cold form blister pack:

It comprises of cold forming blister laminate of aluminium foil (one side bright, soft tempered, plain, dull side lacquered to oriented polyamide film; bright side lacquer laminated to PVC film) with a backing of hard tampered, heat sealable aluminium foil coated with heat seal lacquer and of printable quality.

Carton contains 4 tablets packed in blister pack. Each blister strip contains 4 tablets.

Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

a SUN PHARMA company

14 Lautre Road

Stormill, Ext. 1, Roodepoort

Johannesburg,

1724.

8. REGISTRATION NUMBERS

RAVIAG 25: 45/7.1.5/0872

RAVIAG 50: 45/7.1.5/0873

RAVIAG 100: 45/7.1.5/0874

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

RAVIAG 25: 27 November 2014

RAVIAG 50: 27 November 2014

RAVIAG 100: 27 November 2014

10. DATE OF REVISION OF THE TEXT

26 April 2022

Namibia: Raviag 50: NS2 Reg. no.: 15/7.1/0004 Raviag100: NS2 Reg. no.: 15/7.1/0005