SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form)
RAVIAG 25 (Film Coated tablets)
RAVIAG 50 (Film Coated tablets)
RAVIAG 100 (Film Coated tablets)

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.

RAVIAG tablets contain the following inactive ingredients: Anhydrous calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and Opadry red (film coating material).

PHARMACOLOGICAL CLASSIFICATION
A 7.1.5 Vasodilators – peripheral

PHARMACOLOGICAL ACTION
Pharmacodynamic properties:
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.

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 liters, 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.
Metabolism:
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.

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 = 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.

INDICATIONS
RAVIAG is indicated only for the treatment of erectile dysfunction.
THIS PRODUCT IS NOT AN APHRODISIAC.

CONTRA-INDICATIONS
RAVIAG is contra-indicated in patients with a known hypersensitivity to sildenafil or to any of the other components of the tablet.
RAVIAG potentiates the hypotensive effects of acute and chronic nitrates (see **PHARMACOLOGICAL ACTION**), and its co-administration with nitric oxide donors or nitrates in any form either regularly or intermittently is therefore contra-indicated. Doctors should discuss with patients the contra-indication of **RAVIAG** with concurrent organic nitrates.
RAVIAG is also contra-indicated in:
- Severe hepatic impairment (e.g. cirrhosis).
- Severe renal impairment (e.g. creatinine clearance < 30 ml/min).
- Concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, ritonavir, saquinavir, ketoconazole, itraconazole).

Plasma levels of sildenafil, at 24 hours post dose, have been found to be 3 to 8 times higher in the following patients: age > 65, hepatic impairment (e.g. cirrhosis), severe renal impairment (e.g. creatine clearance < 30 ml/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin); than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely co-administered at this time point.

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 **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.
Sildenafil 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 **INTERACTIONS**). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating **RAVIAG** treatment. Doctors 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) 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. 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.

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.
Medical practitioners should discuss with patients the contra-indication of **RAVIAG** with regular and/or intermittent use of organic nitrates.
Medical practitioners should discuss with patients the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular risk factors. Patients who experience symptoms (e.g. angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their medical practitioner.
Medical practitioners should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently with **RAVIAG**. 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 may result.

Effects on the 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.

INTERACTIONS
Effects of other medicines on RAVIAG
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.
In vivo studies: 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. However with co-administration of sildenafil with azithromycin (500 mg daily for 3 days), no evidence was found of an effect on the AUC or other kinetic parameters of sildenafil.
Co-administration of a 100 mg single dose of sildenafil with saquinavir (1200 mg three times daily) or ritonavir (500 mg twice daily) resulted in respectively a 210 % and 1000 % increase in AUC of sildenafil. (Sildenafil had no effect on either the saquinavir or ritonavir pharmacokimetics.)
Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.
Population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, ACE inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).
Effects of RAVIAG on other medicines
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} >150 microM). Given sildenafil peak plasma concentrations of approximately 1 microM after recommended doses, it is unlikely that sildenafil will alter the clearance of substrates of these isoenzymes.
No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9. Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).
Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.
No interaction was seen when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients.
No difference was seen in the side effect profile in patients taking sildenafil with and without anti-hypertensive medication.
Sildenafil was shown to potentiate the hypotensive effect of acute and chronic nitrates. Therefore, use of nitrates or nitric oxide donors with **RAVIAG** is contra-indicated (see **CONTRA-INDICATIONS**).
Symptomatic hypotension may occur when **RAVIAG** is administered concomitantly with alpha-blockers (see **WARNINGS and SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION
RAVIAG is not indicated for use in women.
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.

DOSAGE AND DIRECTIONS FOR USE
RAVIAG tablets are for oral administration.
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.
Use in the Elderly and in Patients with Mild to Moderately Impaired Renal or Hepatic Function:
A starting dose of 25 mg is recommended in these patients, since higher plasma levels may increase incidence of adverse events (see **PHARMACOLOGICAL ACTION**).
Use in Children:
RAVIAG is not indicated for use in children.

SIDE-EFFECTS
Infections and infestations
Frequent: Flu syndrome.
Less frequent: Respiratory tract infection, infection, Herpes simplex, pharyngitis, bronchitis, sinusitis, urinary tract infection, laryngitis.
Blood and the lymphatic system disorders
Less frequent: Anaemia and leukopenia.
Immune system disorders
Less frequent: Allergic reaction.
Frequency unknown: Hypersensitivity reactions (including skin rashes).
Metabolism and nutrition disorders
Less frequent: Gout, unstable diabetes, hyperglycaemia, hyperuricaemia, hypoglycaemic reaction, and 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 and hypoaesthesia.
Frequency unknown: 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 and eye pain.
Frequency unknown: 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 and 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 unknown: Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular dysrhythmia (see **WARNINGS and SPECIAL PRECAUTIONS**).
Vascular disorders
Frequent: Flushing.
Less frequent: Hypotension, epistaxis, shock, postural hypotension.
Frequency unknown: Hypotensive events after the use of **RAVIAG** in combination with alpha blockers, syncope, cerebrovascular haemorrhage, transient ischaemic attack and hypertension (see **WARNINGS and SPECIAL PRECAUTIONS**).
Respiratory, thoracic and mediastinal disorders
Frequent: Rhinitis (nasal congestion).
Less frequent: Asthma, dyspnoea, respiratory disorder, increased sputum, increased cough.
Gastro-intestinal 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, connective tissue and bone 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 unknown: 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
See **SIDE-EFFECTS**.
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.

IDENTIFICATION
RAVIAG 25
Red coloured, rounded triangular shaped, film coated tablets, with **'S21'** engraved on side and plain on the other.
RAVIAG 50
Red coloured, rounded triangular shaped, film coated tablets, with **'S22'** engraved on side and plain on the other.
RAVIAG 100
Red coloured, rounded triangular shaped, film coated tablets, with **'S23'** engraved on side and plain on the other.

PRESENTATION
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 inner side foil should be odorless.
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 the 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. Each blister strip contains 4 tablets.

STORAGE INSTRUCTIONS
Store at or below 30 °C, in the original pack.
The blisters should be kept in the carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
RAVIAG 25: 45/7.1.5/0872
RAVIAG 50: 45/7.1.5/0873
RAVIAG 100: 45/7.1.5/0874

NAME AND BUSSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
RANBAXY (SA) (PTY) LTD
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DATE OF PUBLICATION OF THE PACKAGE INSERT
27 November 2014

SKEDULERINGSTATUS: S4

EIENDOMSNAAM (en doseervorm)
RAVIAG 25 (Filmbedekte tablette)
RAVIAG 50 (Filmbedekte tablette)
RAVIAG 100 (Filmbedekte tablette)

SAMESTELLING
RAVIAG 25
Elke filmbedekte tablet bevat sildenafilsitraat ekwivalent aan 25 mg sildenafil.
RAVIAG 50
Elke filmbedekte tablet bevat sildenafilsitraat ekwivalent aan 50 mg sildenafil.
RAVIAG 100
Elke filmbedekte tablet bevat sildenafilsitraat ekwivalent aan 100 mg sildenafil.

RAVIAG tablette bevat die volgende onaktiewe bestanddele: Anhidriese kalsiumwaterstoffosfaat, natriumkroskarmellose, magnesiumstearaat, mikrokristallyne sellulose en rooi Opadry (filmbedekkingsmateriaal).

FARMAKOLOGIESE KLASSIFIKASIE
A 7.1.5 Perifere vasodilators

FARMAKOLOGIESE WERKING
Farmakodinamiese eienskappe:
Sildenafil is 'n selektiewe inhibeerder van fosfodiesterase tipe 5 (PDE5), 'n ensiem verantwoorderlik vir die afbreking van sikliese guanosienmonofosfaat (cGMP) in die corpus cavernosum. Deur die vermindering in die effek van PDE5, fasiliteer sildenafil die effek van stikstofoksied gedurende seksuele stimulasie wat lei tot verhoogde vlakke van cGMP, gladdespier verslapping, en wat die toevloei van bloed in die corpus cavernosum toelaat wat 'n ereksie bewerkstellig.
Sildenafil herstel belemmerde ereksiefunksie deur die bloedvloei na die penis te verhoog, met gevolglik 'n natuurlike respons op seksuele stimulering.

Farmakokinetiese eienskappe:
Absorpsie:
Sildenafil word vinnig geabsorbeer. Maksimum waargenome plasmakonsentrasie word binne 30 tot 120 minute (gemiddeld 60 minute) na mondelikse dosering in die vastende toestand bereik. Die gemiddelde absolute orale biobeskikbaarheid is 40 % (reikwydte 25-63 %). Die orale farmakokinetika is in verhouding oor die aanbevole dosisreeks (25-100 mg).
'n Maaltyd hoog in vet verminder die absorpsietempo met 'n gemiddelde vertraging in T_{maks} van 60 minute en 'n gemiddelde afname in C_{maks} van 29 %.
Verspreiding:
Die gemiddelde vastevlak volume van distribusie (Vvv) vir sildenafil is 105 liter, wat dui op die verspreiding in die weefsels. Sildenafil en sy hoof sirkulerende N-desmetiel metaboliet word albei ongeveer 96 % aan plasmaproteïene gebind. Proteïenbinding is onafhanklik van totale geneesmiddelkonsentrasies.
By gesonde vrywilligers was minder as 0,0002 % van die sildenafil 90 minute na dosering teenwoordig in die semen.
Metabolisme:
Sildenafil word deur die CYP3A4 (hoofroete) en CYP2C9 (ondergeskikte roete) deur mikrosomale lewerisoënsieme opgeruim.
Sildenafil word deur *N*-demetilering na 'n aktiewe metaboliet omgeskakel met soortgelyke eienskappe as dié van die moederverbinding, sildenafil, en 'n *in vitro* sterkte van ongeveer 50 % as dié van die moederverbinding teenoor PDE5. Plasmakonsentrasies van hierdie metaboliet is ongeveer 40 % van dit wat waargeneem word deur sildenafil. Die *N*-desmetiel metaboliet word verder gemetaboliseer, met 'n terminale halfleeftyd van ongeveer 4 uur.
Eliminasie:
Sildenafil word as metaboliete hoofsaaklik in die feses uitgeskei na orale toediening (ongeveer 80 %) en tot 'n mindere mate in die urine (ongeveer 13 %).
Die totale liggaamsopruiming van sildenafil is 4 ℓ/h met 'n gevolglike terminale fase half-leeftyd van 3-5 uur.

Farmakokinetika by Spesiale Pasiëntgroepe:
- Bejaardes: Gesonde bejaarde vrywilligers (65 jaar of ouer) het 'n verlaagde opruiming van sildenafil, met vry plasmakonsentrasies ongeveer 40 % hoër as dié waargeneem by gesonde jonger vrywilligers (18-45 jaar).
- Nierontoereikendheid: By vrywilligers met ligte (CLcr = 50-80 ml/min) en matige (CLcr = 30-49 ml/min) nierontoereikendheid, was die farmakokinetika van 'n enkel mondelikse dosis van sildenafil (50 mg) onveranderd. By vrywilligers met ernstige (CLcr ≤ 30 ml/min) nierontoereikendheid, was sildenafil-opruiming verminder met gevolglike verhogings in AOK (100 %) en C_{maks} (88 %) vergeleke met vrywilligers van ooreenstemmende ouderdom met geen nierontoereikendheid nie.
- Lewerontoereikendheid: By vrywilligers met lewersirrose (Child-Pugh A en B) was sildenafil-opruiming verminder, met gevolglike verhogings in die AOK (84 %) en C_{maks} (47 %) vergeleke met vrywilligers van ooreenstemmende ouderdom met geen lewerontoereikendheid nie.

INDIKASIES
RAVIAG word slegs vir die behandeling van erektiele disfunksie aangedui.
HIERDIE PRODUK IS NIE 'N GESLAGSPRIKKELMIDDEL NIE.

KONTRA-INDIKASIES
RAVIAG is teenaangedui by pasiënte met 'n bekende hipersensitiwiteit teenoor sildenafil of teenoor enige van die ander komponente van die tablet.
RAVIAG versterk die hipotensiewe effekte van akute en chroniese nitrate (sien **FARMAKOLOGIESE WERKING**), en die gesamentlike toediening daarvan met stikstofoksiedskenkers of nitrate in enige vorm of gereeld of onderbroke, is daarom teenaangewese. Dokters behoort die kontra-indikasie van **RAVIAG** gelyktydig met organiese nitrate gebruik met pasiënte te bespreek.
RAVIAG is ook teenaangedui by:
- Ernstige lewerontoereikendheid (bv. sirrose).
- Ernstige nierontoereikendheid (bv. kreatinienopruiming < 30 ml/min).
- Gelyktydige gebruik van kragtige sitochroom P450 3A4 inhibeerders (bv. eritromisien, ritonavir, sakwinanavir, ketokonasool, itrakonasool).

By die volgende pasiënte: ouderdom > 65, lewerontoereikendheid (bv. sirrose), ernstige nierontoereikendheid (bv. kreatinienopruiming < 30 ml/min), en gelyktydige gebruik van kragtige sitochroom P450 3A4 inhibeerders (bv. eritromisien) is sildenafil-plasmavlakke van sildenafil, 24 uur na dosering, 3 tot 8 keer hoër as by gesonde vrywilligers gevind. Alhoewel sildenafil-plasmavlakke 24 uur na 'n dosis heelwat laer is as by piekkonsentrasie, is dit onbekend of nitrate op hierdie tydstip veilig toegedien kan word.

WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS

Daar is 'n moontlikheid van hartrisiko met seksuele aktiwiteit vir pasiënte met voorafbestaande kardiovaskulêre siekte. Behandelings vir erektiele disfunksie, insluitende **RAVIAG**, moet dus nie gebruik word by mans waar seksuele aktiwiteit vanweë hul onderliggende kardiovaskulêre toestand, nie raadsaam is nie.

'n Deeglike mediese geskiedenis en fisiese ondersoek moet uitgevoer word om erektiele disfunksie te diagnoseer, om onderliggende moontlike oorsake te bepaal, en om geskikte behandeling te identifiseer.
Sildenafil besit sistemiese vasodilatoriese eienskappe wat verbygaande verminderings in rugliggende bloeddruk by gesonde vrywilligers tot gevolg gehad het. Dokters moet deeglik besin of pasiënte met onderliggende kardiovaskulêre siekte, veral in kombinasie met seksuele aktiwiteit, nadelig deur sodanige vaatverwyderende effekte geaffekteer kan word.
Pasiënte met verhoogde vatbaarheid vir vasodilatore, sluit dié in met linker ventrikulêre uitvloei-obstruksie (soos aortiese stenose of hipertrofiese obstruktiewe kardiomiopatie), of dié met die sindroom van veelvuldige sisteem-atrofie wat manifesteer as ernstige belemmerde outonome beheer van bloeddruk.
Gesamentlike toediening van **RAVIAG** aan pasiënte wat alfa-blokkeermiddel-terapie gebruik, kan tot simptomatiese hipotensie by vatbare individue lei (sien **INTERAKSIES**). Ten einde die moontlikheid van ontwikkeling van posturale hipotensie te minimaliseer, behoort pasiënte hemodinamies-stabiel op alfa-blokkeerder- terapie te wees voordat met **RAVIAG**-behandeling begin word. Dokters behoort pasiënte te adviseer oor wat om te doen in geval van posturale hipotensiewe simptome.
Ernstige kardiovaskulêre voorvalle, insluitende miokardiale infarksie, skielike sterfte as gevolg van die hart, ventrikulêre aritmieë, serebrovaskulêre bloeding, verbygaande isgemiese aanval en hipertensie, is aangemeld.
Die veiligheid en doeltreffendheid van **RAVIAG** is nie vasgestel in die volgende pasiëntgroepe nie; indien voorgeskryf, moet dit met omsigtigheid gedoen word.
- Pasiënte wat aan miokardiale infarksie gely het, beroerte, of lewensbedreigende aritmieë binne die afgelope 6 maande gely het;
- Pasiënte met rustende hipotensie (BD <90/50) of hipertensie (BD >170/110);
- Pasiënte met hartversaking of koronêre hartvatsiekte met gevolglike onstabiele angina;
- Pasiënte met retinitis pigmentosa ('n minderheid van hierdie pasiënte het genetiese afwykings van retinal fosfodiësterase).

Verlengde ereksie langer as 4 uur en priapisme (pynlike ereksies wat langer as 6 uur duur) is aangemeld. Die pasiënt moet onmiddellik mediese hulp verkry in die geval van 'n ereksie wat langer as 4 uur duur. Indien priapisme nie onmiddellik behandel word nie, kan penisweefsel beskadig word en permanente verlies van potensie kan volg.
RAVIAG moet met sorg gebruik word by pasiënte met anatomiese wanvorming van die penis (soos hoekvorming, kavernosale fibrose of Peyronie se siekte), of by pasiënte met toestande wat kan lei tot priapisme (soos sekelselanemie, veelvuldige miëloom of leukemie).
Die veiligheid en doeltreffendheid van kombinasies van **RAVIAG** met ander behandelings vir erektiele disfunksie is nie bestudeer nie. Daarom word die gebruik van sulke kombinasies nie aanbeveel nie.
Interaksies tussen **RAVIAG** en ander antihipertensiewe middels is nie bestudeer nie.
RAVIAG het geen effek op bloedingstyd nie, insluitende tydens gesamentlike toediening met aspirien.
In vitro studies met menslike plaatjies dui daarop dat sildenafil die anti-aggregasie effek van natriumnitroprussied ('n stikstofoksied-skenker) potensieer. Veiligheidsinligting oor die toediening van **RAVIAG** aan pasiënte met bloedingsversteurings of aktiewe peptiese ulserasie is nie beskikbaar nie. **RAVIAG** behoort daarom met sorg aan hierdie pasiënte toegedien te word.
Nie-arteritiese anterior isgemiese optiese neuropatie (NAION) met effense verlies van visie of onomkeerbare blindheid is aangemeld met die gebruik van selektiewe fosfodiësterase tipe-5 inhibeerders insluitende sildenafil (soos bevat in **RAVIAG**). Dit wil voorkom asof NAION 'n klas-effek van hierdie medisynes is. Die meeste van hierdie pasiënte besit risikofaktore soos 'n lae kelk-tot-skyf-verhouding ("oorlaaide skyf"), bo 50-jarige ouderdom, diabetes, hipertensie, koronêre vatsiekte, hiperlipidemie en rook. **RAVIAG** behoort nie aan sulke pasiënte toegedien te word nie.

INLIGTING AAN PASIËNTE
Die gebruik van **RAVIAG** verskaf geen beskerming teen seksueel oordraagbare siektes nie. Berading aan pasiënte oor beskermende maatreëls wat nodig is om te beskerm teen seksueel oordraagbare siektes, insluitende die menslike immuniteitsgebrekvirus (MIV/VIGS) moet oorweeg word. Voorsorgmaatreëls teen ongewenste swangerskap moet getref word.
Dokters behoort newe-effekte van **RAVIAG** met gereëlde en/of onderbroke gebruik van organiese nitrate met pasiënte te bespreek.
Dokters behoort die moontlike hartrisiko van seksuele aktiwiteit by pasiënte met voorafbestaande kardiovaskulêre risikofaktore met pasiënte te bespreek. Pasiënte wat simptome (bv. angina pectoris, duiseligheid, naarheid) by aanvang van seksuele aktiwiteit ervaar, behoort aangeraai te word om hul te weerhou van verdere aktiwiteit en behoort die episode met hul dokter te bespreek.
Dokters behoort pasiënte te waarsku dat verlengde ereksies wat langer as 4 uur duur en priapisme (pynlike ereksies wat langer as 6 uur duur) selde met **RAVIAG** aangemeld is. In die geval waar 'n ereksie langer as 4 uur duur, moet die pasiënt onmiddellik mediese hulp verkry. Indien priapisme nie dadelik behandel word nie, kan penisweefsel beskadig word wat tot permanente verlies van potensie kan lei.

Effekte op die vermoë om te bestuur en masjinerie te gebruik:
Aangesien duiseligheid en veranderde visie mag voorkom met **RAVIAG** gebruik, moet pasiënte bewus wees van hoe hulle op **RAVIAG** reageer en moet versigtigheid aan die dag gelê word voordat 'n motor bestuur word, gevaarlike masjinerie hanteer word of gevaarlike take uitgevoer word.

INTERAKSIES
Effekte van ander medisynes op RAVIAG
Plasmasildenafil konsentrasies word met 56 % verhoog wanneer simetidien (800 mg), 'n nie-spesifieke CYP3A4 inhibeerder, tesame met sildenafil (50 mg) aan gesonde vrywilligers toegedien word.
Sildenafil-opruiming is verminder wanneer gelyktydig met CYP3A4-inhibeerders toegedien word (soos itrakonasool, ketokonasool, eritromisien, en simetidien). Daar was egter geen verhoogde insidensie van newe-effekte by hierdie pasiënte nie.
In vivo studies: 'n Enkeldosis van 100 mg sildenafil toegedien saam met 500 mg eritromisien twee keer per dag, het 'n 182 % toename in sildenafil sistemiese blootstelling (AOK) by gelykstaat tot gevolg. Geen bewys van die effek op die AOK of ander kinetiese parameter van sildenafil is gevind na gelyktydige toediening van sildenafil met asitromisien (500 mg daagliks vir 3 dae).
Gelyktydige toediening van 'n 100 mg enkeldosis van sildenafil met sakwinavir (1200 mg drie keer per dag) of ritonavir (500 mg twee keer per dag) het respektiewelik 'n 210 % en 1000 % toename in die AOK van sildenafil tot gevolg. (Sildenafil het geen effek op óf die sakwinavir óf ritonavir farmakokinetika nie.)
Enkel teensuurdosisse (magnesiumhidroksied/aluminiumhidroksied) het nie die biobeskikbaarheid van sildenafil verander nie.
Farmakokinetiese analise van populasies het geen effek getoon op sildenafil farmakokinetika met gelyktydige medikasie nie, wanneer gegroepeer as CYP2C9-inhibeerders (soos tolbutamied, warfarien), CYP2D6-inhibeerders (soos selektiewe serotonien heropname-inhibeerders, trisikliese antidepressante), tiasied- en verwante diuretika, lus- en kaliumsparende diuretika, AOE-inhibeerders, kalsiumkanaalblokkeerders, beta-adrenoreseptor-antagoniste of induseerders van CYP450 metabolisme (soos rifampisien, barbiturate).
Effekte van RAVIAG op ander medisynes
Sildenafil is 'n swak inhibeerder van die sitochroom-P450 isovorme 1A2, 2C9, 2C19, 2D6, 2E1 en 3A4 (IC_{50} >150 µM). Met inagneming van sildenafil se piekplasmakonsentrasies van ongeveer 1 µM na aanbevole dosisse, is dit onwaarskynlik dat sildenafil die opruiming van die substrate van hierdie isoënsieme sal verander.
Geen beduidende interaksies is aangetoon met tolbutamied (250 mg) of warfarien (40 mg), hierdie word albei gemetaboliseer deur CYP2C9. Sildenafil (50 mg) het nie die verhoogde bloedingstyd veroorsaak deur aspirien (150 mg) versterk nie.
Sildenafil (50 mg) het nie die hipotensiewe effekte van alkohol in gesonde vrywilligers met gemiddelde maksimum alkoholvlakke van 80 mg/dl versterk nie.
Geen interaksie is waargeneem wanneer sildenafil (100 mg) saam met amlodipien aan hipertensiewe pasiënte toegedien word nie.
Geen verskil is waargeneem in die newe-effekprofiel by pasiënte wat sildenafil saam met of sonder anti-hipertensiewe medikasie geneem het nie.
Daar is aangetoon dat sildenafil die hipotensiewe effek van acute en chroniese nitrate versterk. Daarom is die gebruik van nitrate of stikstofoksied skenkers saam met **RAVIAG** teenaangedui (sien K**ONTRA-INDIKASIES**).
Simptomatiese hipotensie kan voorkom wanneer **RAVIAG** gelyktydig met alfa-blokeermiddels toegedien word (sien **WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS**).

SWANGERSKAP EN LAKTASIE
RAVIAG is nie aangedui vir gebruik by vrouens nie.
Voortplantingstudies in rotte en hase het geen teratogeniese effekte, belemmering van vrugbaarheid of newe-effekte op peri/postnatale ontwikkeling getoon na mondelingse toediening van sildenafil nie.
Enkel mondelingse dosisse van 100 mg sildenafil by gesonde vrywilligers het geen effek op die spermbeweeglikheid of morfologie gehad nie.

DOSIS EN GEBRUIKSAANWYSINGS
RAVIAG tablette is vir mondelingse toediening.
Gebruik by Volwassenes:
Die aanbevole dosis is 50 mg een keer per dag soos benodig, geneem een uur voor seksuele aktiwiteit. Die dosis kan verhoog word tot 100 mg of verlaag word tot 25 mg afhangende van die verdraagbaarheid en doeltreffendheid. Die maksimum daaglikse dosis is 100 mg. Die maksimum dosisfrekwensie is een keer per dag.
Gebruik by Volwassenes en by Pasiënte met Ligte tot Matige Belemmerde Nier- of Lewerfunksie:
'n Aanvangsdosis van 25 mg word aanbeveel by hierdie pasiënte, aangesien hoër plasmavlakke tot 'n verhoogde voorkoms van newe-effekte kan lei (sien **FARMAKOLOGIESE WERKING**).
Gebruik by Kinders:
RAVIAG word nie aanbeveel vir gebruik by kinders nie.

NEWE-EFFEKTE
Infeksies en infestasies
Dikwels: Griepsindroom.
Minder dikwels: Lugweginfeksie, infeksie, Herpes simplex, faringitis, brongitis, sinusitis, urienweginfeksie, laringitis.
Bloed- en die limfatiese stelselversteurings
Minder dikwels: Anemie en leukopenie.
Immuunstelselversteurings
Minder dikwels: Allergiese reaksie.
Voorkoms onbekend: Hipersensitiwiteitsreaksies (insluitende veluitslae).
Metabolisme en voedingsversteurings
Minder dikwels: Jig, onstabiele diabetes, hiperglukemie, hiperurisemie, hipoglukemiese reaksie, en hipernatremie.
Psigiatriese versteurings
Minder dikwels: Slaaploosheid, depressie, abnormale drome, anorgasmie.
Senuweestelselversteurings
Dikwels: Hoofpyn, duiseligheid.
Minder dikwels: Ataksie, hipertonie, neuralgie, neuropatie, parestesie, bewerigheid, vertigo, slaperigheid, verminderde reflekse, skeelhoofpyn, miastenie, bewerigheid en hipoëstesie.
Voorkoms onbekend: Stuipe, herhaaldelike stuipe.
Oogversteurings
Dikwels: Abnormale visie (verhoogde persepsie van lig, belemmerde visie), chromatopsie (lig en verbygaande, hoofsaaklik 'n visuele kleurskakering).
Minder dikwels: Konjunktivitis, fotofobie, oogbloeding, katarak, droë oë en oogpyn.
Voorkoms onbekend: Dubbelsig, tydelike verlies van visie/afname in visie, okulêre rooiheid of bloedbelope voorkoms, okulêre branderigheid, okulêre swelling/druk, verhoogde intra-okulêre druk, retinale vaskulêre siekte of bloeding, glasvog losmaking/sametrekking en paramakulêre edeem. Nie-arteritiese anterior isgemiese, optiese neuropatie (NAION) wat permanente verlies van sig kan veroorsaak.
Oor- en labirintversteurings
Minder dikwels: Tinnitus, oorpyn, doofheid.
Hartversteurings
Dikwels: Palpitasie
Minder dikwels: Angina pectoris, AV-blok, tagikardie, hartstilstand, hartversaking, kardiomiopatie.
Voorkoms onbekend: Ernstige kardiovaskulêre voorvalle, insluitende miokardiale infarksie, skielike sterfte aan die hart, ventrikulêre aritmieë (sien **WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS**).
Vaskulêre versteurings
Dikwels: Blosing.
Minder dikwels: Hipotensie, neusbloeding, skok, posturale hipotensie.
Voorkoms onbekend: Hipotensiewe voorvalle na gebruik van **RAVIAG** in kombinasie met alfa-blokkeermiddels, sinkopee, serebrovaskulêre bloeding, verbygaande isgemiese aanval en hipertensie (sien **WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS**).
Respiratoriese, torakale en mediastinale versteurings
Dikwels: Rinitis (nasale kongestie).
Minder dikwels: Asma, dispnee, respiratoriese versteuring, toename in speeksel, toename in hoes.
Gastro-intestinale versteurings
Dikwels: Dispepsie.
Minder dikwels: Braking, naarheid, glossitis, kolitis, disfagie, gastritis, gastroënteritis, abdominale pyn, esofagitis, stomatitis, droë mond, rektale bloeding, gingivitis, diaree.
Vel- en subkutane weefselversteurings
Minder dikwels: Urtikarie, pruritus, sweet, velulkus, kontakdermatitis, afskilferende dermatitis, gesigsedeem, fotosensitiwiteitsreaksie, uitslag, alopesie, sellulitis.
Muskuloskeletale, bindweefsel- en beenversteurings
Minder dikwels: Artritis, artrose, artralgie, mialgie, tendonruptuur, en tenosinovitis, beenpyn, sinovitis, ledemaat en/of rugpyn.
Renale en urinêre verteurings
Minder dikwels: Sistitis, nokturie, urinêre frekwensie, urinêre inkontinensie en hematurie.
Voortplantingstelsel- en borsversteurings
Minder dikwels: Abnormale ejakulasie, prostaatversteuring, genitale edeem, borsvergroting.
Voorkoms onbekend: Verlengde ereksie, priapisme.
Algemene versteurings en toedienplektoestande
Minder dikwels: Astenie, fotosensitiwiteitsreaksie, skok, pyn, dors, koue rillings, edeem, perifere edeem, borspyn.
Ondersoeke
Minder dikwels: Abnormale elektrokardiogram, abnormale lewerfunksie-toetse.
Besering, Vergiftiging en Prosedure komplikasies
Minder dikwels: Toevallige besering/val.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
Sien **NEWE-EFFEKTE**.
In gevalle van oordosering is behandeling simptomaties en ondersteunend.
Daar word nie verwag dat nierdialise opruiming sal versnel nie, aangesien sildenafil grotendeels aan plasmaproteïene gebind word en nie in die urine uitgeskei word nie.

IDENTIFIKASIE
RAVIAG 25
Rooikleurige, geronde driehoekvormige, filmbedekte tablette, met **'S21'** gegraveer op die sykant en skoon op die ander kant.
RAVIAG 50
Rooikleurige, geronde driehoekvormige, filmbedekte tablette, met **'S22'** gegraveer op die sykant en skoon op die ander kant.
RAVIAG 100
Rooikleurige, geronde driehoekvormige, filmbedekte tablette, met **'S23'** gegraveer op die sykant en skoon op die ander kant.

AANBIEDING
Die **RAVIAG** tablette word verpak in PVC/PE/PVdC stolpverpakking (triplex stolpverpakking), deursigtige PVC stolpverpakking en kouevorm stolpverpakking.
Deursigtige PVC Stolpverpakking:-
Helder PVC-film met harde getemperede, hitte-verseëlbare aluminiumfoelie bedek met reuklose hitteseëllak aan die binnekant van die foelie.
PVC/PE/PVdC stolpverpakking (Triplex stolpverpakking):-
Die pak bestaan uit helder deursigtige PVC-film, gelamineer met poli-etileen (PE) en bedek met PVdC aan die binnekant, met 'n rugkant van harde getemperde hitte-verseëlbare aluminiumfoelie bedek met hitteseëllak.
Kouevorm stolpverpakking:-
Dit bestaan uit kouevorm stolplaminaat van aluminiumfoelie (een kant helder, saggetemper, skoon, dowwe kant gelak aan geöriënteerde poliamiedfilm; helder kant lakgelamineer aan PVC-film) met 'n rugkant van harde getemperde hitte-verseëlbare aluminiumfoelie bedek met hitteseëllak waarop drukwerk gedoen kan word.
Karton bevat 4 tablette verpak in 'n stolpstrook. Elke stolpstrook bevat 4 tablette.

BEWARINGSINSTRUKSIES
Bewaar by of benede 30 °C, in die oorspronklike verpakking.
Die stolpstroke moet in die karton gehou word tot benodig vir gebruik.
HOU BUITE DIE BEREIK VAN KINDERS.

REGISTRASIENOMMERS
RAVIAG 25: 45/7.1.5/0872
RAVIAG 50: 45/7.1.5/0873
RAVIAG 100: 45/7.1.5/0874

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