1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PROFESSIONAL INFORMATION HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

STENDRIL 25 mg film coated tablets

STENDRIL 50 mg film coated tablets

STENDRIL 100 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

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

Contains sugar (lactose 1,89 mg/tablet)

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

Contains sugar (lactose 3,78 mg/tablet)

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

Contains sugar (lactose 7,56 mg/tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

STENDRIL 25 mg: Pale blue to blue, round film-coated tablet, debossed with ‘25’ on one side and ‘SL’ on other side.

STENDRIL 50 mg: Pale blue to blue, capsule shaped film-coated tablets, debossed with ‘SL50’ on one side and plain on the other side.

STENDRIL 100 mg: Pale blue to blue, capsule shaped film-coated tablets, debossed with ‘SL100’ on one side and plain on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

STENDRIL is indicated for adults 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 oral dose is 50 mg, taken as needed once daily, approximately one hour before sexual intercourse. The dose may be increased to 100 mg or decreased to 25 mg, depending on the efficacy and tolerance. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once daily.

The following factors are associated with increased plasma levels of sildenafil, as contained in STENDRIL:

- Age > 65 (40 % increase in AUC)
- Hepatic impairment (e.g. cirrhosis, 80 %)
- Severe renal impairment (creatinine clearance < 30 mL/min, 100 %).

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 STENDRIL 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 STENDRIL. 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), STENDRIL should not be used concomitantly with these medicines.

STENDRIL administration is contraindicated in patients who use nitric oxide donors or nitrates in any form, as it was shown to potentiate the hypotensive effects of nitrates (see section 4.3**)**.

Paediatric population:

STENDRIL is not indicated for use in children.

Method of administration

For oral use

4.3 Contraindications

Known hypersensitivity to sildenafil or to any of the other excipients listed in section 6.1.

Administration of STENDRIL 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, STENDRIL was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its co- administration with nitric oxide donors or nitrates in any form, either regularly or intermittently, is therefore contraindicated. Medical practitioners should discuss the contraindication of STENDRIL with concurrent organic nitrates with patients.

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Medicines for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

STENDRIL 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 (see section 4.4).

Severe hepatic impairment (e.g. cirrhosis).

Severe renal impairment (e.g. creatinine clearance <30 mL/min) not on haemodialysis or continuous ambulatory peritoneal dialysis.

Concomitant use of **STENDRIL** with potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, cimetidine, ritonavir, saquinavir, ketoconazole, itraconazole) is contraindicated.

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

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 sildenafil, as contained in STENDRIL, 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 sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, 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.

STENDRIL, 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.

STENDRIL has systemic vasodilatory properties that resulted in transient decrease 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 **STENDRIL** to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating **STENDRIL** treatment. Medical practitioners should advise patients what to do in the event of postural hypotensive symptoms.

STENDRIL should be prescribed with caution in the following patients:

- 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). There is no safety information on the administration of **STENDRIL** to patients with retinitis pigmentosa, therefore, STENDRIL should be administered with caution to these patients.

Patients should seek immediate medical assistance in the event of an erection that persists longer than 4 hours. Priapism (painful erections lasting longer than 6 hours) should be treated immediately, as penile tissue damage and permanent loss of potency could result.

STENDRIL 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).

Combinations of **STENDRIL** with other treatments for erectile dysfunction is not recommended as the safety and efficacy of such combinations have not been studied. Therefore, the use of such combinations is inadvisable.

STENDRIL should be administered with caution to patients with bleeding disorders or active peptic ulceration.

STENDRIL has no effect on bleeding time, including during co-administration with aspirin.

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 **STENDRIL**). 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. **STENDRIL** should not be given to these patients.

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

STENDRIL *contains lactose*. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take **STENDRIL**.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on Stendril

Inhibitors of cytochrome P450 (CYP) isoforms 3A4 (major route of sildenafil) and 2C9 (minor route of sildenafil) isoenzymes may reduce sildenafil clearance which include the following: Cimetidine, erythromycin, itraconazole, ketoconazole and HIV-protease inhibitors, such as saquinavir.

Inducers of cytochrome P450 (CYP) isoform 3A4 may increase the metabolism and clearance of sildenafil, such as rifampicin.

Ritonavir increases the plasma concentration of sildenafil significantly and such combinations should not be given (see section 4.3).

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

No effect of concomitant medication on sildenafil pharmacokinetics acting as CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors (SSRIs), 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) has been noted.

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 **STENDRIL** or its major circulating metabolite.

Effects of Stendril on other medicines

Stendril may potentiate the hypotensive effect of acute and chronic nitrates. Therefore, the concomitant use of sildenafil and nitrates or nitric oxide donors is contraindicated (see section 4.3).

Concomitant use of **STENDRIL** and other antihypertensive medicines may potentiate the antihypertensive effect of these medicines. Symptomatic postural hypotension has been reported in patients who receive concomitant therapy with doxazosin and sildenafil. This includes reports of dizziness and light-headedness, but not syncope.

Sildenafil, as contained in Stendril did not potentiate the increase in bleeding time caused by aspirin.

No significant interactions were shown between sildenafil and tolbutamide (250 mg) or warfarin (40 mg), both being metabolised by CYP2C9 isoenzyme.

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

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

Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

STENDRIL is not indicated for use in women.

Sildenafil was not found to be teratogenic, embryotoxic or foetotoxic in animal studies.

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

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 5.1).

4.7 Effects on ability to drive and use machines

STENDRIL can lead to dizziness and altered vision and patients should be aware how they react to **STENDRIL** and exercise caution before driving a vehicle, operating hazardous machinery or performing hazardous tasks.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and vision blurred.

Tabulated summary of adverse reactions

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency.

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations		Rhinitis	
Immune system disorders		Hypersensitivity	
Nervous system disorders	Headache Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure,* Seizure recurrence,* Syncope
Eye disorders	Visual colour distortions*, Visual disturbance, Vision blurred	Lacrimation disorders***, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis	Non-arteritic anterior ischaemic optic neuropathy (NAION), * Retinal vascular occlusion,* Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect,

			Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discoloration Retinal detachment
Ear and labyrinth disorders		Vertigo, Tinnitus	Deafness
Cardiac disorders		Tachycardia, Palpitations	Sudden cardiac death,* Myocardial infarction, Ventricular arrhythmia,* Atrial fibrillation, Unstable angina
Vascular disorders	Flushing, Hot flush	Hypertension, Hypotension	
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Epistaxis, Sinus congestion	Throat tightness, Nasal oedema, Nasal dryness
Gastrointestinal disorders	Nausea, Dyspepsia	Gastro oesophageal reflux disease, Vomiting, Abdominal pain upper, Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders		Rash	Stevens-Johnson Syndrome (SJS),* Toxic Epidermal Necrolysis (TEN)*
Musculoskeletal and connective tissue disorders		Myalgia, Pain in extremity	
Renal and urinary disorders		Haematuria	
Reproductive system and breast disorders			Penile haemorrhage, Priapism,* Haematospermia, Erection increased
General disorders and administration site conditions		Chest pain, Fatigue, Feeling hot	Irritability
Investigations		Heart rate increased	

*****Reported during post-marketing surveillance only

**Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythropsia and Xanthopsia

***Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction 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 800mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction. ATC Code: G04B E03.

A 7.1.5 Vasodilators – peripheral

Mechanism of action

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

Sildenafil is a selective phosphodiesterase type 5 (PDE5) inhibitor, an enzyme responsible for degrading cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. Sildenafil enhances the effect of nitric oxide (NO) on the corpus cavernosum tissue during sexual stimulation, resulting in increased cGMP levels, causing the smooth muscle to relax, allowing blood flow into the corpus

cavernosum producing an erection. Sildenafil increases blood flow to the penis, in response to sexual stimulation and thereby restores impaired erectile function.

Pharmacodynamic effects

Studies in vitro have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Sildenafil has no direct relaxant

effect on isolated human corpus cavernosum but enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, during sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum allowing the inflow of blood.

5.2 Pharmacokinetic properties

Absorption

Sildenafil is rapidly absorbed after an oral dose with a mean absolute bioavailability of about 40 %. Peak plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The oral pharmacokinetics of sildenafil is proportional over the recommended dose range (25 - 100 mg). A high fat meal reduces absorption of sildenafil as shown by a mean reduction in the maximum plasma concentration (C_{max}) of 29 % and a mean delay in the time to peak concentration (T_{max}) of 60 minutes.

Distribution

The mean steady state volume of distribution (Vss) for sildenafil is 105 litres. Sildenafil and its major circulating N-desmethyl metabolite, exhibit high (96 %) plasma protein binding, independent of total medicine concentrations. Less than 0,0002 % of sildenafil remained in the semen of healthy volunteers at 90 minutes after dosing.

Biotransformation

Hepatic metabolism of sildenafil is predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) microsomal isoenzymes. Sildenafil is converted by N-demethylation to an active metabolite with a PDE selectivity profile similar to sildenafil. The terminal half-life of the N-desmethyl metabolite is approximately 4 hours.

Elimination

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

Pharmacokinetics in special populations

Elderly

Healthy elderly volunteers, 65 years or over, cleared sildenafil less effectively from the plasma than did normal healthy volunteers, 18 to 45 years of age, as shown by a 40 % increase of AUC in older adults.

Renal insufficiency

Sildenafil clearance was reduced in volunteers with mild Cl_{cr} (creatinine clearance) = 50·80 ml/min) and moderate (Cl_{cr}=30-49 ml/min) renal impairment, the pharmacokinetics of a single oral dose of **STENDRIL** (50 mg) were not altered. In volunteers with severe (Cl_{cr} < 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

Sildenafil clearance was reduced in volunteers with hepatic cirrhosis (Child-Pugh A and B), resulting in increases in AUC by 84 % and C_{max} by 47 % compared to age-matched volunteers with no hepatic impairment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

microcrystalline cellulose

Silica, Colloidal Anhydrous

calcium hydrogen phosphate (anhydrous)

croscarmellose sodium

magnesium stearate

Film coat:

Hydroxypropylmethyl cellulose

titanium dioxide

lactose monohydrate

triacetin

indigo carmine aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25°C.

Store in the original package in order to protect from moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

STENDRIL 25 mg film-coated tablets PVC/Aluminium blisters in cartons of 2, 4, 8 or 12, 28 tablets**.**

STENDRIL 50 mg film-coated tablets PVC/Aluminium blisters in cartons of 2, 4, 8 or 12, 28 tablets**.**

STENDRIL 100 mg film-coated tablets PVC/Aluminium blisters in cartons of 2, 4, 8 or 12, 28 tablets**.**

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

P.O. Box 431

Pinetown 3600

8 REGISTRATION NUMBER(S)

STENDRIL 25: 56/7.1.5/0826

STENDRIL 50: 54/7.1.5/0034

STENDRIL 100: 54/7.1.5/0035

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 April 2023

10 DATE OF REVISION OF THE TEXT

15 February 2024