SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

TIDALIS 5

TIDALIS 20

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **TIDALIS 5** film coated tablet contains 5 mg tadalafil.

Each **TIDALIS 20** film coated tablet contains 20 mg tadalafil.

Contains lactose:

Each **5** mg film coated tablet contains 81,7 mg lactose (as monohydrate).

Each **20** mg film coated tablet contains 326.8 mg lactose (as monohydrate)

Contains sodium:

Each 5 mg film coated tablet contains 0.02 mmol (0.55 mg) sodium.

Each 20 mg film coated tablet contains 0.10 mmol (2.20 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

TIDALIS 5 mg: Yellow to light yellow, round shaped, bevelled edge, coated tablets debossed with ‘L 337’ on one side and plain on the other side.

TIDALIS 20 mg: Yellow to light yellow, round shaped, bevelled edge, coated tablets debossed with 'L 339' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIDALIS is indicated for the treatment of erectile dysfunction. In order for **TIDALIS** to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology

In adult men:
The recommended dose is 5 mg taken once a day at approximately the same time of day.
The recommended maximum dose of **TIDALIS** is 20 mg taken prior to anticipated sexual activity and without regard to food.

TIDALIS 20 mg can be taken up to 36 hours and as early as 16 minutes prior to sexual activity. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness.

The maximum recommended dosing frequency is once per day

Special populations

Renal impairment
Dosage adjustments are not required in patients with mild or moderate renal impairment. Once-a-day dosing of **TIDALIS** is not recommended in patients with severe renal impairment.

Paediatric population

TIDALIS is not indicated for children under the age of 18 years.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, tadalafil, or to any of the excipients of **TIDALIS** listed in section 6.1.
- Administration of **TIDALIS** to patients who are using any form of organic nitrate.
- Patients with severe hepatic insufficiency (Child-Pugh Class C).
- Loss of vision in one eye or both eyes 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)
- Previous experience of unilateral or bilateral decrease or loss of hearing with or without associated vestibular symptoms.

4.4 Special warnings and precautions for use

Before treatment with **TIDALIS**

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Sexual activity carries a potential cardiac risk for patients with pre-existing cardiovascular disease. Prior to initiating any treatment for erectile dysfunction, medical practitioners should consider the cardiovascular status of their patients. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3). **TIDALIS** should not be used in men with cardiac disease for

whom sexual activity is inadvisable.
It is not known if tadalafil is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular

Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing **TIDALIS**, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.
- In patients receiving concomitant antihypertensive medicinal products, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

In patients who are taking alpha1 blockers, concomitant administration of **TIDALIS** may lead to symptomatic hypotension in some patients (see Section 4.5). The combination of tadalafil and doxazosin is not recommended. In a clinical pharmacology study of 18 healthy volunteers who received a single dose of **TIDALIS**, no symptomatic hypotension was observed with simultaneous administration of tamsulosin, an α-[1A] blocker (see section 4.5).

The use of **TIDALIS** is not recommended in the following patients:

- with myocardial infarction within the last 90 days.
- with unstable angina or angina occurring during sexual intercourse.
- with New York Heart Association Class 2 or greater heart failure in the last 6 months.
- with uncontrolled dysrhythmia, hypotension (< 90/50 mm Hg), or uncontrolled hypertension
- with a stroke within the last 6 months.

Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should report the episode to their medical practitioner

Vision

Non-arteritic anterior ischemic optic neuropathy (NAION) is a cause of decreased vision including permanent loss of vision. Visual defects and cases of NAION have been reported in connection with the intake of **TIDALIS** and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, he should stop taking **TIDALIS** and consult a medical practitioner immediately (see section 4.3). Medical practitioner should also discuss with patients that individuals who have already experienced NAION are at increased risk of NAION.

Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Patients should be advised to stop taking **TIDALIS** and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events may be accompanied by tinnitus and dizziness.

Renal and hepatic impairment

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.
Once-a-day administration has not been evaluated in patients with hepatic insufficiency.

Priapism and anatomical deformation of the penis

Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

TIDALIS 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).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing **TIDALIS** to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin), as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

TIDALIS and other treatments for erectile dysfunction

The safety and efficacy of combinations of **TIDALIS** and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take **TIDALIS** in such combinations.

Lactose

Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take **TIDALIS**

Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicines on tadalafil

Cytochrome P450 inhibitors

TIDALIS is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and Cmax by 15 %, relative to the AUC and Cmax values for tadalafil alone. Ketoconazole (400 mg daily), increased tadalafil 20 mg single-dose exposure (AUC) 4-fold and Cmax by 22 %.

Transporters

The role of transporters (for example, p-glycoprotein) in the disposition of tadalafil is not known. Therefore, there is the potential of medicine interactions mediated by inhibition of transporters.

Cytochrome P450 inducers

A selective CYP3A4 inducer, rifampicin (rifampicin, 600 mg daily), reduced tadalafil single-dose exposure (AUC) by 88 % and Cmax by 46 %, relative to the AUC and Cmax values for tadalafil alone. This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. It can be expected that concomitant administration of other CYP3A4 inducers, such as phenobarbitone, phenytoin and carbamazepine may also decrease plasma concentrations of tadalafil.
Ritonavir (200 mg twice daily) an inhibitor of CYP3A4, 2C9, 2C19 and 2D6, increased tadalafil single-dose exposure (AUC) by 124 % with no change in Cmax. Although specific interactions have not been studied, other HIV protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors such as erythromycin and itraconazole, would likely increase tadalafil exposure.

Antacids

Simultaneous administration of an antacid (magnesium hydroxide/aluminium hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H_2-antagonists

An increase in gastric pH resulting from administration of nizatidine, an H_2 antagonist, had no significant effect on tadalafil pharmacokinetics.

Effects of tadalafil on other medicines

Nitrates

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see Section 4.3).

Anti-hypertensives

Tadalafil has systemic vasodilatory properties and may augment the blood pressure lowering effects of antihypertensive medicines. Additionally, in patients taking multiple antihypertensive medicines whose hypertension was not well controlled, greater reductions in blood pressure were observed. These reductions were not associated with hypotensive symptoms in the vast majority of patients. Appropriate clinical advice should be given to patients when they are treated with antihypertensive medications and tadalafil.
Tadalafil had no clinically significant effect on blood pressure changes due to tamsulosin, an α-adrenergic receptor blocking agent.
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Some patients experienced dizziness. Therefore, this combination is not recommended (see section 4.4).

CYP1A2 substrates

Tadalafil had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline, a CYP1A2 substrate.

Ethinylestradiol and terbutaline

Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol

Tadalafil did not affect alcohol concentrations and alcohol did not affect tadalafil concentrations. At high doses of alcohol (0,7 g/kg), the addition of tadalafil did not induce statistically significant mean blood pressure decreases. In some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0,6 g/kg), hypotension was not observed and dizziness occurred

with similar frequency to alcohol alone.

Cytochrome P450 metabolised medicines

Tadalafil does not inhibit or induce CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

CYP2C9 substrates (e.g. R-warfarin)

Tadalafil had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin

Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Antidiabetic medicinal products

Specific interaction studies with antidiabetic medicinal products were not conducted.

Riociguat

Studies have shown an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. Riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination. Riociguat should not be used concomitantly with PDE5 inhibitors such as tadalafil.

5-alpha reductase inhibitors

No new adverse reactions were identified when tadalafil was co-administered with finasteride.

However, as a formal interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

4.6 Fertility, pregnancy and lactation

TIDALIS is not indicated for use by women.

Safety and efficacy of **TIDALIS** in pregnancy and lactation have not been established.

Pregnancy

TIDALIS should not be used during pregnancy.

Breastfeeding

TIDALIS should not be used during breast feeding.

Fertility

Although animal studies indicate impairment of fertility, subsequent clinical studies suggest this is unlikely in humans. A decrease in sperm concentration has however, been seen in some men (see Section 5.3).

4.7 Effects on ability to drive and use machines

TIDALIS has a negligible influence on the ability to drive or use machines. However, there have been reports of dizziness, therefore patients should be aware of how they react to **TIDALIS** before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking tadalafil for the treatment of erectile dysfunction were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Immune system disorders	*Less frequent*	Hypersensitivity reactions Angioedema[2]
Nervous system disorders	*Frequent*	Headache
	Less frequent	Dizziness, stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures, Transient amnesia
Eye disorders	*Less frequent*	Blurred vision, Sensations described as eye pain. Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders	*Less frequent*	Tinnitus Sudden hearing loss
Cardiac disorders[1]	*Less frequent*	Tachycardia, palpitations Myocardial infarction, Unstable angina pectoris[2], Ventricular dysrythmia[2]
Vascular disorders	*Frequent*	Flushing

	Less frequent	Hypotension[3], Hypertension
Respiratory, thoracic and mediastinal disorders	*Frequent*	Nasal congestion
	Less frequent	Dyspnoea, epistaxis
Gastrointestinal disorders	*Frequent*	Dyspepsia
	Less frequent	Abdominal pain, Vomiting, Nausea, Gastro- oesophageal reflux
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Back pain, Myalgia, Pain in extremity
Renal and urinary disorders	*Less frequent*	Haematuria
Reproductive system and breast disorders	*Less frequent*	Prolonged erections Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions	*Less frequent*	Chest pain[1], Peripheral oedema, Fatigue Facial oedema[2], Sudden cardiac death[1,2]

(1) Most of the patients had pre-existing cardiovascular risk factors (see Section 4.4).

(2) Post marketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.

(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse events

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Although there is limited data in patients over 65 years of age, in clinical trials with tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **TIDALIS** is important. It allows continued monitoring of the benefit/risk balance of **TIDALIS**. Healthcare professionals 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

Single doses of up to 500 mg have been given to healthy subjects and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 7.1.5 Vasodilators-peripheral
Pharmacotherapeutic group: Urological, Drugs used in erectile dysfunction
ATC code: G04BE08

Mechanism of action
Tadalafil improves impaired erectile function by increasing blood flow to the penis, in response to sexual stimulation.
Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects
Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases.
Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

5.2 Pharmacokinetic properties

Absorption
Tadalafil is well absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing.
The rate and extent of absorption of tadalafil are not influenced by food. Thus, tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 L. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Less than 0,0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

Tadalafil is predominantly metabolised by the cytochrome P450 CYP3A4 isoform.
The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13 000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination

The mean half-life is 17,5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity / non-linearity

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2,5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Special populations

Elderly

Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal impairment

In subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment, tadalafil exposure (AUC) was higher than in healthy subjects. In subjects with renal insufficiency, including those on haemodialysis, tadalafil exposure AUC was higher than in healthy subjects.

Hepatic impairment

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects. No dose adjustment is required in these patients. No data are available in patients with severe hepatic impairment (Child-Pugh Class C).

Patients with diabetes

Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicone dioxide, croscarmellose sodium, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, methylene chloride, opadry yellow, povidone, sodium lauryl sulphate.

6.2 Incompabilities

Not applicable.

6.3 Shelf life:

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture and sunlight.

Keep out of reach of children.

6.5 Nature and contents of the container

TIDALIS tablets 5mg and 20 mg are both available in Blister pack of unprinted aluminum foil and unprinted CFB foil and blister pack of unprinted aluminum foil and clear PVC/Alcar film of 2, 4, 8 or 10 tablets per strip in printed unit carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals
Crownwood Office Park
100 Northern Parkway
Ormonde
Johannesburg
2091
South Africa

8. REGISTRATION NUMBER

Will be allocated by SAHPRA upon registration.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Will be allocated by SAHPRA upon registration.

10. DATE OF REVISION OF THE TEXT